DEPARTMENT OF THE NAVY
NAVAL MEDICAL COMMAND
WASHINGTON, D.C. 20372-5120

IN REPLY REFER TO
NAVMEDCOMINST 6230.1A
MEDCOM-24
1 Oct 87

NAVMEDCOM INSTRUCTION 6230.1A

From: Commander, Naval Medical Command
To: Ships and Stations Having Medical Department Personnel

Subj: VIRAL HEPATITIS PREVENTION

Ref: (a) NAVMED P-5038, Control of Communicable Diseases in Man (NOTAL)
(b) NAVMED P-5010, Chapter 1
(c) OPNAVINST 1700.9A (NOTAL)
(d) NAVMEDCOMINST 6220.2 (NOTAL)
(e) NAVMEDCOMINST 6320.3B

Encl: (1) Centers for Disease Control. Recommendations for Protection Against Viral Hepatitis. MMWR 1985; 34:22 (A
(2) Centers for Disease Control. Update on Hepatitis B Prevention, MMWR 1987; 36:23 (A
(3) Other Medical Department Responsibilities, Information and Sources of Consultation for the Prevention and Control of Viral Hepatitis and Management of Hepatitis B Virus (HBV) Carriers (A
(4) Algorithm for Prophylaxis Involving Hepatitis in Food Handlers
(5) Graphic Presentation of Serological Markers, Clinical Symptoms, and Transmission of Viral Hepatitis (R

1. Purpose. To provide policy and recommendations for the prevention and control of viral hepatitis among Navy and Marine Corps personnel and their dependents, Military Sealift Command personnel, and personnel of other services (including Federal civilian employees) and their dependents serving, traveling, or attending activities aboard facilities under sponsorship of the Navy or Marine Corps. To provide guidance for the management and disposition of hepatitis B virus (HBV) carriers. (R

2. Cancellation. NAVMEDCOMINST 6230.1.

3. Background. Military campaigns have been compromised seriously when viral hepatitis occurred in operational units. Most recently, hepatitis was a common health hazard encountered by United States (U. S.) forces during World War II, the Korean conflict, and in Vietnam. Viral hepatitis continues to pose a frequent hazard to personnel in some areas. Medical Department personnel must be knowledgeable of and use the most current information and recommendations available for the prevention and control of the various types of viral hepatitis. References (A

(a) through (e) and enclosures (1) through (5) cover current preventive measures and other information needed for effective hepatitis prevention programs. The information in the enclosures must be adopted as general guidelines. Operational and geographic situations, however, may require modification or elaboration of any or all of these guidelines as directed by the appropriate fleet commander in chief (CINC), commanding general fleet marine force (CG FMF), or commanders of geographic naval medical commands, and as recommended by the area Navy environmental and preventive medicine unit (NAVENPVNTMEDU). Reference (d) provides specific guidelines for reporting suspected or confirmed viral hepatitis cases in a Disease Alert Report (DAR) via priority message. A viral hepatitis DAR must include the patient's itinerary during the previous 3 months.

4. Action

a. Commanders, commanding officers, and officers in charge must:

(1) Direct the implementation of recommended control measures against viral hepatitis when advised to do so by competent medical authority.

(2) Ensure that all command personnel receive adequate instruction in sanitation, personal hygiene, and enteric disease prevention in hepatitis A (HAV)-endemic areas.

(3) Ensure that all command personnel receive adequate instruction on risks of sexual contacts or potential blood exposure in highly HBV-endemic areas.

b. Medical Department Personnel. For the prevention and control of viral hepatitis, Medical Department personnel must take action as directed or recommended in applicable portions of enclosures (1) through (4).

J. S. CASSELLS

Stocked:
CO, NAVPUBFORMCEN
5801 Tabor Ave.
Phila., PA 19120-5099

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*Recommendation of the Immunization Practices Advisory Committee (ACIP)*

# Recommendations for Protection Against Viral Hepatitis

*The following statement updates all previous recommendations on use of immune globulins for protection against viral hepatitis (*MMWR *1981;30:423-35) and use of hepatitis B vaccine and hepatitis B immune globulin for prophylaxis of hepatitis B (*MMWR *1982;31:317-28 and* MMWR *1984;33:285-90).*

## INTRODUCTION

The term "viral hepatitis" is commonly used for several clinically similar diseases that are etiologically and epidemiologically distinct (*1*). Two of these, hepatitis A (formerly called infectious hepatitis) and hepatitis B (formerly called serum hepatitis) have been recognized as separate entities since the early 1940s and can be diagnosed with specific serologic tests. The third, currently known as non-A, non-B hepatitis, is probably caused by at least two different agents, and lacking specific diagnostic tests, remains a disease diagnosed by exclusion. It is an important form of acute viral hepatitis in adults and currently accounts for most post-transfusion hepatitis in the United States. An epidemic type of non-A, non-B hepatitis, which is probably spread by the fecal-oral route and is different from the types seen in the United States, has been described in parts of Asia and North Africa (*2*).

A fourth type of hepatitis, delta hepatitis, has recently been characterized as an infection dependent on hepatitis B virus. It may occur as a coinfection with acute hepatitis B infection or as superinfection of a hepatitis B carrier (*3*).

## HEPATITIS SURVEILLANCE

Approximately 21,500 cases of hepatitis A, 24,300 cases of hepatitis B, 3,500 cases of non-A, non-B hepatitis, and 7,100 cases of hepatitis type unspecified were reported in the United States in 1983. Most cases of each type occur among young adults. Since reporting from many localities is incomplete, the actual number of hepatitis cases occurring annually is thought to be several times the reported number.

## IMMUNE GLOBULINS

Immune globulins used in medical practice are sterile solutions of antibodies (immunoglobulins) from human plasma. They are prepared by cold ethanol fractionation of large plasma pools and contain 10%-18% protein. In the United States, plasma is primarily obtained from professional donors. Only plasma shown to be free of hepatitis B surface antigen (HBsAg) is used to prepare immune globulins.

Immune globulin (IG) (formerly called "immune serum globulin," ISG, or "gamma globulin") produced in the United States contains antibodies against the hepatitis A virus (anti-HAV) and the hepatitis B surface antigen (anti-HBs). Tests of IG lots prepared since 1977 indicate that both types of antibody have uniformly been present. Hepatitis B immune globulin (HBIG) is an IG prepared from plasma containing high titers of anti-HBs.

*ACIP: Viral Hepatitis – Continued*

Neither IG nor HBIG commercially available in the United States transmits hepatitis or other viral infections. There is no evidence that the causative agent of AIDS (human T-lymphotropic virus type III/lymphadenopathy-associated virus [HTLV-III/LAV]) has been transmitted by IG or HBIG (*4*).

Serious adverse effects from immune globulins administered as recommended have been exceedingly rare. Standard immune globulins are prepared for intramuscular use and should not be given intravenously. Two preparations for intravenous use in immunodeficient and other selected patients have recently become available in the United States but are not recommended for hepatitis prophylaxis. Immune globulins are not contraindicated for pregnant women.

**HEPATITIS A**

Hepatitis A is caused by the hepatitis A virus (HAV), a 27-nm ribonucleic acid (RNA) agent that is a member of the picornavirus family. The illness caused by HAV characteristically has an abrupt onset with fever, malaise, anorexia, nausea, abdominal discomfort, and jaundice. Severity is related to age. In children, most infections are asymptomatic, and illness is usually not accompanied by jaundice. Most infected adults become symptomatically ill with jaundice. Fatality among reported cases is infrequent (about 0.6%).

Hepatitis A is primarily transmitted by person-to-person contact, generally through fecal contamination. Transmission is facilitated by poor personal hygiene, poor sanitation, and intimate (intrahousehold or sexual) contact. Common-source epidemics from contaminated food and water also occur. Sharing utensils or cigarettes or kissing are not believed to transmit the infection.

The incubation period of hepatitis A is 15-50 days (average 28-30). High concentrations of HAV ($10^8$ particles/g) are found in stools of infected persons. Fecal virus excretion reaches its highest concentration late in the incubation period and early in the prodromal phase of illness, and diminishes rapidly once jaundice appears. Greatest infectivity is during the 2-week period immediately before the onset of jaundice. Viremia is of short duration; virus has not been found in urine or other body fluids. A chronic carrier state with HAV in blood or feces has not been demonstrated. Transmission of HAV by blood transfusion has occurred but is rare.

The diagnosis of acute hepatitis A is confirmed by finding IgM-class anti-HAV in serum collected during the acute or early convalescent phase of disease. IgG-class anti-HAV, which appears in the convalescent phase of disease and remains detectable in serum thereafter, apparently confers enduring protection against disease. Commercial tests are available to detect IgM anti-HAV and total anti-HAV in serum.

Although the incidence of hepatitis A in the United States has decreased over the last 15 years, it is still a common infection in older children and young adults. About 38% of reported hepatitis cases in this country are attributable to hepatitis A.

**Recommendations for IG prophylaxis of hepatitis A**. Numerous field studies conducted in the past 4 decades confirm that IG given before exposure or during the incubation period of hepatitis A is protective against clinical illness (*5-7*). Its prophylactic value is greatest (80%-90%) when given early in the incubation period and declines thereafter (*7*).

**Preexposure prophylaxis**. The major group for whom preexposure prophylaxis is recommended is international travelers. The risk of hepatitis A for U.S. citizens traveling abroad varies with living conditions, incidence of hepatitis A infection in areas visited, and length of stay (*8,9*). In general, travelers to developed areas of western Europe, Japan, and Australia are at no greater risk of infection than in the United States. In contrast, travelers to developing countries may be at significant risk of infection. In such areas, the best way to prevent hepatitis A and other enteric diseases is to avoid potentially contaminated water or food. Drinking water (or beverages with ice) of unknown purity and eating uncooked shellfish or uncooked fruits or vegetables that are not peeled (or prepared) by the traveler should be avoided.

IG is recommended for travelers to developing countries if they will be eating in settings of poor or uncertain sanitation (some restaurants or homes) or will be visiting extensively with local persons, especially young children, in settings with poor sanitary conditions. Persons who plan to reside in developing areas for long periods should receive IG regularly if they anticipate exposure as described above or will be living in rural areas with poor sanitation.

For such travelers, a single dose of IG of 0.02 ml/kg is recommended if travel is for less than 2 months. For prolonged travel, 0.06 ml/kg should be given every 5 months. For persons who require repeated IG prophylaxis, screening for total anti-HAV antibodies before travel may be useful to define susceptibility and eliminate unnecessary doses of IG in those who are immune.

**Postexposure prophylaxis**. A serologic test for the diagnosis of acute hepatitis A is now widely available. Since only 38% of acute hepatitis cases in the United States result from hepatitis A, serologic confirmation of hepatitis A in the index case is recommended before treatment of contacts. Serologic screening of contacts for anti-HAV before giving IG is not recommended because screening is more costly than IG and would delay its administration.

IG should be given as soon as possible after exposure; giving IG more than 2 weeks after exposure is not indicated.

Specific recommendations for IG prophylaxis of hepatitis A depend on the nature of the HAV exposure:

1. *Close personal contact.* IG is recommended for all household and sexual contacts of persons with hepatitis A.
2. *Day-care centers.* Day-care facilities with children in diapers can be important settings for HAV transmission (*10-12*). IG should be administered to all staff and attendees of day-care centers or homes if: (a) one or more hepatitis A cases are recognized among children or employees; or (b) cases are recognized in two or more households of center attendees. When an outbreak (hepatitis cases in three or more families) occurs, IG should also be considered for members of households whose diapered children attend. In centers not enrolling children in diapers, IG need only be given to classroom contacts of an index case.
3. *Schools.* Contact at elementary and secondary schools is usually not an important means of transmitting hepatitis A. Routine administration of IG is not indicated for pupils and teachers in contact with a patient. However, when epidemiologic study clearly shows the existence of a school- or classroom-centered outbreak, IG may be given to those who have close personal contact with patients.
4. *Institutions for custodial care.* Living conditions in some institutions, such as prisons and facilities for the developmentally disabled, favor transmission of hepatitis A. When outbreaks occur, giving IG to residents and staff who have close contact with patients with hepatitis A may reduce the spread of disease. Depending on the epidemiologic circumstances, prophylaxis can be limited in extent or can involve the entire institution.
5. *Hospitals.* Routine IG prophylaxis for hospital personnel is not indicated. Rather, sound hygienic practices should be emphasized. Staff education should point out the risk of exposure to hepatitis A and emphasize precautions regarding direct contact with potentially infective materials (*13*).

*ACIP: Viral Hepatitis – Continued*

Outbreaks of hepatitis A among hospital staff occur occasionally, usually in association with an unsuspected index patient who is fecally incontinent. Large outbreaks have occurred among staff and family contacts of infected infants in neonatal intensive-care units. In outbreaks, prophylaxis of persons exposed to feces of infected patients may be indicated.

6. *Offices and factories.* Routine IG administration is not indicated under the usual office or factory conditions for persons exposed to a fellow worker with hepatitis A. Experience shows that casual contact in the work setting does not result in virus transmission.
7. *Common-source exposure.* IG might be effective in preventing foodborne or waterborne hepatitis A if exposure is recognized in time. However, IG is not recommended for persons exposed to a common source of hepatitis infection after cases have begun to occur in those exposed, since the 2-week period during which IG is effective will have been exceeded.

If a foodhandler is diagnosed as having hepatitis A, common-source transmission is possible but uncommon. IG should be administered to other foodhandlers but is usually not recommended for patrons. However, IG administration to patrons may be considered if (a) the infected person is directly involved in handling, without gloves, foods that will not be cooked before they are eaten; (b) the hygienic practices of the foodhandler are deficient; and (c) patrons can be identified and treated within 2 weeks of exposure. Situations where repeated exposures may have occurred, such as in institutional cafeterias, may warrant stronger consideration of IG use.

For postexposure IG prophylaxis, a single intramuscular dose of 0.02 ml/kg is recommended.

**HEPATITIS B**

Hepatitis B virus (HBV) infection is a major cause of acute and chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma worldwide. The frequency of HBV infection and patterns of transmission vary markedly in different parts of the world. In the United States, western Europe, and Australia, it is a disease of low endemicity, with only 0.1%-0.5% of the population being virus carriers and infection occurring primarily during adulthood. In contrast, HBV infection is highly endemic in China and Southeast Asia, sub-Saharan Africa, most Pacific islands, and the Amazon Basin; in these areas, 5%-15% of the population carry the virus, and most persons acquire infection at birth or during childhood. In other parts of the world, HBV is moderately endemic, and 1%-4% of persons are HBV carriers. Recommendations for prophylaxis of hepatitis B will vary in accordance with local patterns of HBV transmission. The recommendations that follow are intended for use in the United States.

Hepatitis B infection is caused by the HBV, a 42-nm, double-shelled deoxyribonucleic acid (DNA) virus. Several well-defined antigen-antibody systems have been associated with HBV infection (Table 1). HBsAg, formerly called "Australia antigen" or "hepatitis-associated antigen," is found on the surface of the virus and on accompanying 22-nm spherical and tubular forms. HBsAg can be identified in serum 30-60 days after exposure to HBV and persists for variable periods. The various subtypes (adr, adw, ayw, ayr) of HBsAg provide useful epidemiologic markers. Antibody against HBsAg (anti-HBs) develops after a resolved infection and is responsible for long-term immunity. Anti-HBc, the antibody to the core antigen (an internal component of the virus), develops in all HBV infections and persists indefinitely. IgM anti-HBc appears early in infection and persists for 6 or more months; it is a reliable marker of acute or recent HBV infection. The hepatitis B e antigen (HBeAg) is a third antigen, presence of which correlates with HBV replication and high infectivity. Antibody to HBeAg (anti-HBe) develops in most HBV infections and correlates with lower infectivity.

*ACIP: Viral Hepatitis – Continued*

The onset of acute hepatitis B is generally insidious. Clinical symptoms and signs include various combinations of anorexia, malaise, nausea, vomiting, abdominal pain, and jaundice. Skin rashes, arthralgias, and arthritis can also occur. Overall fatality rates for reported cases generally do not exceed 2%. The incubation period of hepatitis B is long—45-160 days (average 60-120).

**TABLE 1. Hepatitis nomenclature**

| Abbreviation | Term | Comments |
|---|---|---|
| | **Hepatitis A** | |
| HAV | Hepatitis A virus | Etiologic agent of "infectious" hepatitis; a picornavirus; single serotype. |
| Anti-HAV | Antibody to HAV | Detectable at onset of symptoms; lifetime persistence. |
| IgM anti-HAV | IgM class antibody to HAV | Indicates recent infection with hepatitis A; positive up to 4-6 months after infection. |
| | **Hepatitis B** | |
| HBV | Hepatitis B virus | Etiologic agent of "serum" or "long-incubation" hepatitis; also known as Dane particle. |
| HBsAg | Hepatitis B surface antigen | Surface antigen(s) of HBV detectable in large quantity in serum; several subtypes identified. |
| HBeAg | Hepatitis B e antigen | Soluble antigen; correlates with HBV replication, high titer HBV in serum, and infectivity of serum. |
| HBcAg | Hepatitis B core antigen | No commercial test available. |
| Anti-HBs | Antibody to HBsAg | Indicates past infection with and immunity to HBV, passive antibody from HBIG, or immune response from HBV vaccine. |
| Anti-HBe | Antibody to HBeAg | Presence in serum of HBsAg carrier suggests lower titer of HBV. |
| Anti-HBc | Antibody to HBcAg | Indicates past infection with HBV at some undefined time. |
| IgM anti-HBc | IgM class antibody to HBcAg | Indicates recent infection with HBV; positive for 4-6 months after infection. |
| | **Delta hepatitis** | |
| δ virus | Delta virus | Etiologic agent of delta hepatitis; may only cause infection in presence of HBV. |
| δ-Ag | Delta antigen | Detectable in early acute delta infection. |
| Anti-δ | Antibody to delta antigen | Indicates past or present infection with delta virus. |
| | **Non-A, non-B hepatitis** | |
| NANB | Non-A, non-B hepatitis | Diagnosis of exclusion. At least two candidate viruses; epidemiology parallels that of hepatitis B. |
| | **Epidemic non-A, non-B hepatitis** | |
| Epidemic NANB | Epidemic non-A, non-B hepatitis | Causes large epidemics in Asia, North Africa; fecal-oral or waterborne. |
| | **Immune globulins** | |
| IG | Immune globulin (previously ISG, immune serum globulin, or gamma globulin) | Contains antibodies to HAV, low titer antibodies to HBV. |
| HBIG | Hepatitis B immune globulin | Contains high titer antibodies to HBV |

**HBV infection in the United States**. The estimated lifetime risk of HBV infection in the United States varies from almost 100% for the highest-risk groups to approximately 5% for the population as a whole. An estimated 200,000 persons, primarily young adults, are infected each year. One-quarter become ill with jaundice; more than 10,000 patients require hospitalization; and an average of 250 die of fulminant disease each year. Between 6% and 10% of young adults with HBV infection become carriers. The United States currently contains an estimated pool of 500,000-1,000,000 infectious carriers. Chronic active hepatitis develops in over 25% of carriers and often progresses to cirrhosis. Furthermore, HBV carriers have a risk of developing primary liver cancer that is 12-300 times higher than that of other persons. It is estimated that 4,000 persons die from hepatitis B-related cirrhosis each year in this country and that more than 800 die from hepatitis B-related liver cancer.

The role of the HBV carrier is central in the epidemiology of HBV transmission. A carrier is defined as a person who is HBsAg-positive on at least two occasions at least 6 months apart. Although the degree of infectivity is best correlated with HBeAg-positivity, any person positive for HBsAg is potentially infectious. The likelihood of developing the carrier state varies inversely with the age at which infection occurs. During the perinatal period, HBV transmitted from HBeAg-positive mothers results in HBV carriage in up to 90% of infected infants, whereas 6%-10% of acutely infected adults become carriers.

Carriers and persons with acute infection have highest concentrations of HBV in the blood and serous fluids; less is present in other body fluids, such as saliva and semen. Transmission occurs via percutaneous or permucosal routes. Infective blood or body fluids can be introduced by contaminated needles or through sexual contact. Infection can occur in settings of continuous close personal contact, such as in households or among children in institutions for the mentally retarded, presumably via inapparent or unnoticed contact of infectious secretions with skin lesions or mucosal surfaces. Transmission of infection by transfusion of contaminated blood or blood products has been greatly reduced since the advent of routine screening with highly sensitive tests for HBsAg. HBV is not transmitted via the fecal-oral route or by contamination of food or water.

Serologic surveys demonstrate that, although HBV infection is uncommon among adults in the general population, it is highly prevalent in certain groups. Those at risk, based on the prevalence of serologic markers of infection, are described in Table 2. Immigrants/refugees and their descendants from areas of high HBV endemicity are at high risk of acquiring HBV infection. Homosexually active men and users of illicit injectable drugs are among the highest-risk groups, acquiring infection soon after adopting these lifestyles (10%-20%/year). Inmates of prisons have high prevalence of HBV markers usually because of prior parenteral drug abuse; actual risk of transmission in prisons is also associated with parenteral drug abuse in prisons. Patients and staff in custodial institutions for the mentally retarded are also at increased risk of having HBV infection. Classroom contacts, particularly teachers or instructors, of some deinstitutionalized carriers may also be at higher risk than the general population. Household contacts and sexual partners of HBV carriers are at increased risk, as are hemodialysis patients and recipients of certain pooled plasma products.

There is increased risk for medical and dental workers and related laboratory and support personnel who have contact with blood. Employment in a hospital without exposure to blood carries no greater risk than that for the general population.

**Hepatitis B prophylaxis**. Two types of products are available for prophylaxis against hepatitis B. Hepatitis B vaccine, licensed in 1981, provides active immunization against HBV infection, and its use is recommended for both pre- and postexposure prophylaxis. IG products provide temporary, passive protection and are indicated only in certain postexposure settings.

*ACIP: Viral Hepatitis — Continued*

**IG and HBIG**. IG and HBIG contain different amounts of anti-HBs. IG is prepared from plasma that is not preselected for anti-HBs content. Since 1977, all lots tested have contained anti-HBs at a titer of at least 1:100 by radioimmunoassay (RIA). HBIG is prepared from plasma preselected for high-titer anti-HBs. In the United States, HBIG has an anti-HBs titer of higher than 1:100,000 by RIA. There is no evidence that the causative agent of AIDS (HTLV-III/LAV) has been transmitted by IG or HBIG (*4*).

**Hepatitis B vaccine**. Hepatitis B vaccine licensed in the United States is a suspension of inactivated, alum-adsorbed 22-nm surface antigen particles that have been purified from human plasma by a combination of biophysical (ultracentrifugation) and biochemical procedures. Inactivation is a threefold process using 8M urea, pepsin at pH 2, and 1:4000 formalin. These treatment steps have been shown to inactivate representatives of all classes of viruses found in human blood, including the causative agent of AIDS (HTLV-III/LAV) (*14*). HB vaccine contains 20 $\mu$g/ml of HBsAg protein.

After a series of three intramuscular doses of hepatitis B vaccine, over 90% of healthy adults develop protective antibody (*15,16*). A course of three 10-$\mu$g doses induces antibody in virtually all infants and children from birth through 9 years of age. The deltoid (arm) is the recommended site for hepatitis B vaccination in adults; immunogenicity of vaccine in adults is significantly lower when injections are given in the buttock (81%) (*17*). The immunogenicity of the intradermal route has not yet been clearly established.

Field trials of the U.S.-manufactured vaccine have shown 80%-95% efficacy in preventing infection or hepatitis among susceptible persons (*16,18*). Protection against illness is virtually complete for persons who develop adequate antibody levels* after vaccination. The duration of protection and need for booster doses are not yet defined. However, only 10%-15% of per-

*Adequate antibody is 10 or more sample ratio units (SRU) by RIA or positive by enzyme immunoassay.

**TABLE 2. Prevalence of hepatitis B serologic markers in various population groups**

| Population group | Prevalence of serologic markers of HBV infection: HBsAg (%) | All markers (%) |
|---|---|---|
| **High risk** | | |
| Immigrants/refugees from areas of high HBV endemicity | 13 | 70-85 |
| Clients in institutions for the mentally retarded | 10-20 | 35-80 |
| Users of illicit parenteral drugs | 7 | 60-80 |
| Homosexually active men | 6 | 35-80 |
| Household contacts of HBV carriers | 3-6 | 30-60 |
| Patients of hemodialysis units | 3-10 | 20-80 |
| **Intermediate risk** | | |
| Health-care workers—frequent blood contact | 1-2 | 15-30 |
| Prisoners (male) | 1-8 | 10-80 |
| Staff of institutions for the mentally retarded | 1 | 10-25 |
| **Low risk** | | |
| Health-care workers—no or infrequent blood contact | 0.3 | 3-10 |
| Healthy adults (first-time volunteer blood donors) | 0.3 | 3-5 |

sons who develop adequate antibody after three vaccine doses will lose antibody within 4 years, and among those who lose antibody, protection against viremic infection and liver inflammation appears to persist. Immunogenicity and efficacy of the licensed vaccine in hemodialysis patients is much lower than in normal adults; protection may last only as long as adequate antibody levels persist (*19*).

**Vaccine usage**. Primary vaccination consists of three intramuscular doses of vaccine, with the second and third doses given 1 and 6 months, respectively, after the first. Adults and older children should be given 20 $\mu$g (1.0 ml) per dose, while children under 10 years should receive 10 $\mu$g (0.5 ml) per dose. For patients undergoing hemodialysis and for other immunosuppressed patients, a 40-$\mu$g (2.0-ml) dose should be used. Vaccine doses administered at longer intervals provide equally satisfactory protection, but optimal protection is not conferred until after the third dose. Hepatitis B vaccine should only be given in the deltoid muscle in adults and children or in the anterolateral thigh muscle in infants and neonates. Since hepatitis B vaccine is an inactivated (noninfective) product, it is presumed that there will be no interference with other simultaneously administered vaccines.

Data are not available on the safety of the vaccine for the developing fetus. Because the vaccine contains only noninfectious HBsAg particles, there should be no risk to the fetus. In contrast, HBV infection in a pregnant woman may result in severe disease for the mother and chronic infection for the newborn. Pregnancy should not be considered a contraindication to the use of this vaccine for persons who are otherwise eligible.

**Vaccine storage**. Vaccine should be stored at 2 C-8 C (36 F-46 F) but not frozen. *Freezing destroys the potency of the vaccine.*

**Side effects and adverse reactions.** The most common side effect observed in prevaccination trials was soreness at the injection site. Among an estimated 750,000 vaccinees, approximately 100 episodes of severe illness have been reported after receipt of vaccine. These have included arthralgias, neurologic reactions (such as Guillain-Barré syndrome), and other illnesses. The rate of Guillain-Barré syndrome following HB vaccine does not appear to be significantly increased above that observed in normal adults. Such temporally associated illnesses are not considered to be etiologically related to hepatitis B vaccine.

**Effect of vaccination on carriers and immune persons**. The vaccine produces neither therapeutic nor adverse effects in HBV carriers (*20*). Vaccination of individuals who possess antibodies against HBV from a previous infection is not necessary but will not cause adverse effects. Such individuals will have a postvaccination increase in their anti-HBs levels. Passively acquired antibody, whether from HBIG or IG administration or from the transplacental route, will not interfere with active immunization (*21*).

**Prevaccination serologic screening for susceptibility**. The decision to screen potential vaccine recipients for prior infection depends on three variables: (1) the cost of vaccination; (2) the cost of testing for susceptibility; and (3) the expected prevalence of immune individuals in the group. Figure 1 shows the relative cost-effectiveness of screening, given different costs of screening tests and the expected prevalence of immunity. In constructing the figure, the assumption was made that the cost of three doses of vaccine is $100 and that there are additional costs for administration. For any combination of screening costs and immunity to hepatitis, the cost-effectiveness can be estimated. For example, if the expected prevalence of serologic markers for HBV is over 20%, screening is cost-effective if costs of screening are no greater than $30 per person. If the expected prevalence of markers is less than 8%, and if the costs of screening are greater than $10 per person, vaccination without screening is cost-effective.

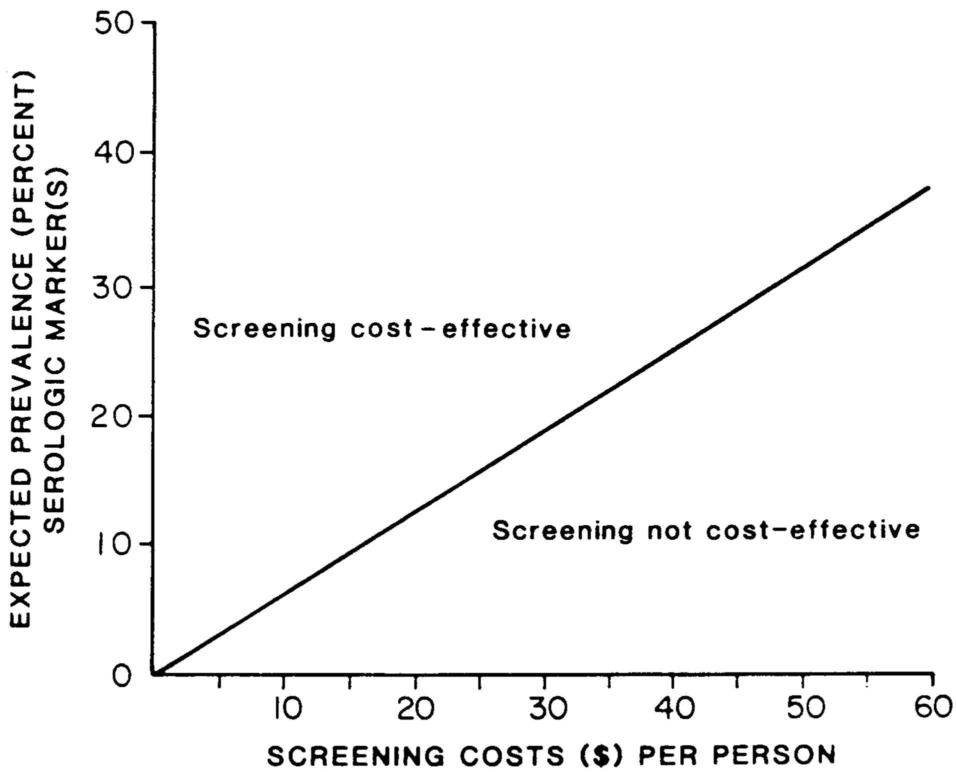
*ACIP: Viral Hepatitis — Continued*

Screening in groups with the highest risk of HBV infection (Table 2) will be cost-effective unless testing costs are extremely high. For groups at intermediate risk, cost-effectiveness of screening may be marginal, and vaccination programs may or may not utilize screening. For groups with a low expected prevalence of HBV serologic markers, such as health professionals in their training years, screening will not be cost-effective.

For routine screening, only one antibody test, either anti-HBc or anti-HBs, need be used. Anti-HBc will identify all previously infected persons, both carriers and noncarriers, but will not discriminate between members of the two groups. Anti-HBs will identify those previously infected, except carriers. For groups expected to have carrier rates of under 2%, such as health-care workers, neither test has a particular advantage. For groups with higher carrier rates, anti-HBc may be preferred to avoid unnecessary vaccination of carriers. If the RIA anti-HBs test is used for screening, a minimum of 10 RIA sample ratio units should be used to designate immunity (2.1 is the usual designation of a positive test). If enzyme immunoassay (EIA) is used, the manufacturers' recommended positive is appropriate.

**Serologic confirmation of postvaccination immunity and revaccination of nonresponders**. When given in the deltoid, hepatitis B vaccine produces protective antibody (anti-HBs) in more than 90% of healthy persons. Testing for immunity following vaccination is not recommended routinely but is advised for persons whose subsequent management depends on

**FIGURE 1. Cost-effectiveness of prevaccination screening of hepatitis B virus vaccine candidates***




*See text for assumptions.

*ACIP: Viral Hepatitis – Continued*

knowing their immune status, such as dialysis patients and staff, and for persons in whom a suboptimal response may be anticipated, such as those who have received vaccine in the buttock.

Revaccination of persons who do not respond to primary series (nonresponders) produces adequate antibody in only one-third when the primary vaccination has been given in the deltoid. Therefore, revaccination of nonresponders to deltoid injection is not recommended routinely. For persons who did not respond to a primary vaccine series given in the buttock, preliminary data from two small studies suggest that revaccination in the arm induces adequate antibody in over 75%. Revaccination should be strongly considered for such persons.

**Preexposure vaccination**. Persons at substantial risk of acquiring HBV infection who are demonstrated or judged likely to be susceptible should be vaccinated. They include:

1. *Health-care workers.* The risk of health-care workers acquiring HBV infection depends on the frequency of exposure to blood or blood products and on the frequency of needlesticks. These risks vary during the training and working career of each individual but are often highest during the professional training period. For this reason, it is recommended that vaccination be completed during training in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions.

   The risk of HBV infection for hospital personnel can vary both among hospitals and within hospitals. In developing specific immunization strategies, hospitals should use available published data about the risk of infection (*22-24*) and may wish to evaluate their own clinical and institutional experience with hepatitis B. Studies in urban centers have indicated that occupational groups with frequent exposure to blood and/or needles have the highest risk of acquiring HBV infection, including (but not limited to) the following groups: medical technologists, operating room staff, phlebotomists and intravenous therapy nurses, surgeons and pathologists, and oncology and dialysis unit staff. Groups shown to be at increased risk in some hospitals include: emergency room staff, nursing personnel, and staff physicians.

   Other health-care workers based outside hospitals who have frequent contact with blood or blood products are also at increased risk of acquiring HBV infection. These include (but are not limited to): dental professionals (dentists, oral surgeons, dental hygienists), laboratory and blood bank technicians, dialysis center staff, emergency medical technicians, and morticians.
2. *Clients and staff of institutions for the mentally retarded.* Susceptible clients and staff who work closely with clients of institutions for the mentally retarded should be vaccinated. Risks for staff are comparable to those for health-care personnel in other high-risk environments. However, the risk in institutional environments is associated, not only with blood exposure, but also with bites and contact with skin lesions and other infective secretions. Susceptible clients and staff who live or work in smaller (group) residential settings with known HBV carriers should also receive hepatitis B vaccine.
3. *Hemodialysis patients.* Numerous studies have established the high risk of HBV transmission in hemodialysis units. Although recent data have shown not only a decrease in the rate of HBV infection in hemodialysis units but also a lower vaccine efficacy in these patients, vaccination is recommended for susceptible patients. Environmental control measures and regular serologic screening (based on immune status) of patients should be maintained.
4. *Homosexually active men.* Susceptible homosexually active men should be vaccinated regardless of their ages or duration of their homosexual practices. It is important to

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vaccinate persons as soon as possible after their homosexual activity begins. Homosexually active women are not at increased risk of sexually transmitted HBV infection.

5. *Users of illicit injectable drugs.* All users of illicit injectable drugs who are susceptible to HBV should be vaccinated as early as possible after their drug use begins.
6. *Recipients of certain blood products.* Patients with clotting disorders who receive clotting factor concentrates have an elevated risk of acquiring HBV infection. Vaccination is recommended for these persons and should be initiated at the time their specific clotting disorder is identified. Screening is recommended for patients who have already received multiple infusions of these products.
7. *Household and sexual contacts of HBV carriers.* Household contacts of HBV carriers are at high risk of acquiring HBV infection. Sexual contacts appear to be at greatest risk. When HBV carriers are identified through routine screening of donated blood, diagnostic testing in hospitals, prenatal screening, screening of refugees, or other screening programs, they should be notified of their status and their susceptible household contacts vaccinated.

   Families accepting orphans or unaccompanied minors from countries of high HBV endemicity should have the child screened for HBsAg, and if positive, family members should be vaccinated.
8. *Other contacts of HBV carriers.* Persons in casual contact with carriers at schools, offices, etc., are at minimal risk of acquiring HBV infection, and vaccine is not routinely recommended for them. However, classroom contacts of deinstitutionalized mentally retarded HBV carriers who behave aggressively or have special medical problems that increase the risk of exposure to their blood or serous secretions may be at risk. In such situations, vaccine may be offered to classroom contacts.
9. *Special high-risk populations.* Some American populations, such as Alaskan Eskimos, native Pacific islanders, and immigrants and refugees from areas with highly endemic disease (particularly eastern Asia and sub-Saharan Africa) have high HBV infection rates. Depending on specific epidemiologic and public health considerations, more extensive vaccination programs should be considered.
10. *Inmates of long-term correctional facilities.* The prison environment may provide a favorable setting for the transmission of HBV because of the frequent use of illicit injectable drugs and homosexual practices. Moreover, it provides an access point for vaccination of parenteral drug abusers. Prison officials should consider undertaking screening and vaccination programs directed at those who abuse drugs before or while in prison.
11. *Heterosexually active persons.* Heterosexually active persons with multiple sexual partners are at increased risk of acquiring HBV infection; risk increases with increasing sexual activity. Vaccination should be considered for persons who present for treatment of sexually transmitted diseases and who have histories of sexual activity with multiple partners.
12. *International travelers.* Vaccination should be considered for persons who plan to reside more than 6 months in areas with high levels of endemic HBV and who will have close contact with the local population. Vaccination should also be considered for short-term travelers who are likely to have contact with blood from or sexual contact with residents of areas with high levels of endemic disease. Hepatitis B vaccination of travelers ideally should begin 6 months before travel in order to complete the full vaccine series; however, a partial series will offer some protection against HBV infection.

*ACIP: Viral Hepatitis – Continued*

**Postexposure prophylaxis for hepatitis B**. Prophylactic treatment to prevent hepatitis B infection after exposure to HBV should be considered in the following situations: perinatal exposure of an infant born to an HBsAg-positive mother; accidental percutaneous or permucosal exposure to HBsAg-positive blood; or sexual exposure to an HBsAg-positive person.

Recent studies have established the relative efficacies of immune globulins and/or hepatitis B vaccine in various exposure situations. For perinatal exposure to an HBsAg-positive, HBeAg-positive mother, a regimen combining one dose of HBIG at birth with the hepatitis B vaccine series started soon after birth is 85%-90% effective in preventing development of the HBV carrier state (*25,27*). Regimens involving either multiple doses of HBIG alone, or the vaccine series alone, have 70%-75% efficacy, while a single dose of HBIG alone has only 50% efficacy (*28*).

For accidental percutaneous exposure or sexual exposure, only regimens including HBIG and/or IG have been studied. A regimen of two HBIG doses, one given after exposure and one a month later, is about 75% effective in preventing hepatitis B following percutaneous exposure; a single dose of HBIG has similar efficacy when used following sexual exposure (*29-31*).

*(Continued on page 329)*

**TABLE I. Summary—cases of specified notifiable diseases, United States**

| Disease | 22nd Week Ending | | | Cumulative, 22nd Week Ending | | |
|---|---|---|---|---|---|---|
| | June 1, 1985 | June 2, 1984 | Median 1980-1984 | June 1, 1985 | June 2, 1984 | Median 1980-1984 |
| Acquired Immunodeficiency Syndrome (AIDS) | 144 | 72 | N | 2,956 | 1,600 | N |
| Aseptic meningitis | 78 | 85 | 85 | 1,544 | 1,665 | 1,665 |
| Encephalitis: Primary (arthropod-borne & unspec.) | 20 | 15 | 15 | 368 | 341 | 341 |
| Post-infectious | 5 | 2 | 1 | 60 | 44 | 44 |
| Gonorrhea: Civilian | 12,436 | 12,203 | 16,749 | 330,873 | 335,310 | 391,294 |
| Military | 204 | 270 | 462 | 7,792 | 8,588 | 11,414 |
| Hepatitis: Type A | 313 | 379 | 379 | 8,831 | 8,734 | 9,468 |
| Type B | 454 | 491 | 396 | 10,354 | 10,451 | 8,772 |
| Non A, Non B | 71 | 81 | N | 1,723 | 1,600 | N |
| Unspecified | 90 | 83 | 153 | 2,273 | 2,018 | 3,551 |
| Legionellosis | 4 | 25 | N | 219 | 231 | N |
| Leprosy | 4 | 6 | 2 | 137 | 98 | 98 |
| Malaria | 17 | 22 | 26 | 303 | 316 | 377 |
| Measles: Total* | 55 | 59 | 59 | 1,235 | 1,476 | 1,476 |
| Indigenous | 50 | 54 | N | 919 | 1,330 | N |
| Imported | 5 | 5 | N | 316 | 146 | N |
| Meningococcal infections: Total | 38 | 46 | 52 | 1,254 | 1,459 | 1,460 |
| Civilian | 38 | 46 | 52 | 1,251 | 1,456 | 1,456 |
| Military | - | - | - | 3 | 3 | 7 |
| Mumps | 49 | 66 | 126 | 1,688 | 1,572 | 2,415 |
| Pertussis | 34 | 27 | 22 | 555 | 870 | 464 |
| Rubella (German measles) | 36 | 14 | 52 | 244 | 351 | 1,331 |
| Syphilis (Primary & Secondary): Civilian | 433 | 458 | 460 | 10,434 | 11,809 | 12,574 |
| Military | 2 | 3 | 3 | 77 | 145 | 157 |
| Toxic Shock syndrome | 5 | 7 | N | 158 | 202 | N |
| Tuberculosis | 288 | 358 | 493 | 8,320 | 8,671 | 10,460 |
| Tularemia | 5 | 18 | 4 | 38 | 65 | 65 |
| Typhoid fever | 13 | 3 | 6 | 118 | 133 | 156 |
| Typhus fever, tick-borne (RMSF) | 33 | 41 | 41 | 105 | 139 | 171 |
| Rabies, animal | 114 | 103 | 157 | 2,096 | 2,100 | 2,805 |

**TABLE II. Notifiable diseases of low frequency, United States**

| | Cum 1985 | | Cum 1985 |
|---|---|---|---|
| Anthrax | - | Leptospirosis (Hawaii 1) | 10 |
| Botulism Foodborne (Calif. 1) | 3 | Plague | 1 |
| Infant | 18 | Poliomyelitis, Total | 2 |
| Other | - | Paralytic (Fla. 1) | 2 |
| Brucellosis (Tex. 7) | 45 | Psittacosis (Calif. 1) | 52 |
| Cholera | - | Rabies, human | - |
| Congenital rubella syndrome | - | Tetanus (Mo. 1) | 24 |
| Congenital syphilis, ages < 1 year | 74 | Trichinosis | 29 |
| Diphtheria | 1 | Typhus fever, flea-borne (endemic, murine) | 1 |

*Four of the 55 reported cases for this week were imported from a foreign country or can be directly traceable to a known internationally imported case within two generations

*ACIP: Viral Hepatitis – Continued*

IG may have some effect in preventing clinical hepatitis B following percutaneous exposures and can be considered as an alternative to HBIG when it is not possible to obtain HBIG.

Recommendations on postexposure prophylaxis are based on the efficacy data discussed above and on the likelihood of future HBV exposure of the person requiring treatment. In perinatal exposure and percutaneous exposure of high-risk health-care personnel, a regimen combining HBIG with hepatitis B vaccine will provide both short- and long-term protection, will be less costly than the two-dose HBIG treatment alone, and is the treatment of choice.

**Perinatal exposure**. One of the most efficient modes of HBV transmission is from mother to infant during birth. If the mother is positive for both HBsAg and HBeAg, about 70%-90% of infants will become infected, and up to 90% of these infected infants will become HBV carriers. If the HBsAg-positive carrier mother is HBeAg-negative, or if anti-HBe is present, transmission occurs less frequently and rarely leads to the HBV carrier state. However, severe acute disease, including fatal fulminant hepatitis in the neonate, has been reported (*32,33*). Prophylaxis of infants from all HBsAg-positive mothers is recommended, regardless of the mother's HBeAg or anti-HBe status.

The efficacy of a combination of HBIG plus the hepatitis B vaccine series has been confirmed in recent studies. Although the following regimen is recommended (Table 3), other schedules have also been effective (*25-27,34*). The major consideration for all these regimens is the need to give HBIG as soon as possible after delivery.

HBIG (0.5 ml [10 $\mu$g]) should be administered intramuscularly after physiologic stabilization of the infant and preferably within 12 hours of birth. Hepatitis B vaccine should be administered intramuscularly in three doses of 0.5 ml (10 $\mu$g) each. The first dose should be given concurrently with HBIG but at a different site. If vaccine is not available at birth, the first vaccine dose may be given within 7 days of birth. The second and third doses should be given 1 month and 6 months, respectively, after the first. Testing for HBsAg and anti-HBs is recommended at 12-15 months to monitor the final success or failure of therapy. If HBsAg is not detectable, and anti-HBs is present, the child has been protected. Testing for anti-HBc is not useful, since maternal anti-HBc may persist for more than 1 year; the utility of testing for IgM anti-HBc is currently being evaluated. HBIG administered at birth should not interfere with oral polio and diphtheria-tetanus-pertussis vaccines administered at 2 months of age.

**Maternal screening**. Since efficacy of the treatment regimen depends on administering HBIG on the day of birth, it is vital that HBsAg-positive mothers be identified before delivery. Mothers belonging to groups known to be at high risk of acquiring HBV infection (Table 4)

**TABLE 3. Hepatitis B virus postexposure recommendations**

| | HBIG | | Vaccine | |
|---|---|---|---|---|
| **Exposure** | **Dose** | **Recommended timing** | **Dose** | **Recommended timing** |
| Perinatal | 0.5 ml IM | Within 12 hours of birth | 0.5 ml (10 $\mu$g) IM | Within 12 hours of birth*; repeat at 1 and 6 months |
| Sexual | 0.06 ml/kg IM | Single dose within 14 days of sexual contact | † | — |

*The first dose can be given the same time as the HBIG dose but at a different site.

†Vaccine is recommended for homosexual men and for regular sexual contacts of HBV carriers and is optional in initial treatment of heterosexual contacts of persons with acute HBV.

should be tested routinely for HBsAg during a prenatal visit. If a mother belonging to a high-risk group has not been screened prenatally, HBsAg screening should be done at the time of delivery, or as soon as possible thereafter, and the infant treated as above if the mother is HBsAg-positive. If the mother is identified as HBsAg-positive more than 1 month after giving birth, the infant should be screened for HBsAg, and if negative, treated with hepatitis B vaccine and HBIG.

The appropriate obstetric and pediatric staff should be notified directly of HBsAg-positive mothers, so the staff may take appropriate precautions to protect themselves and other patients from infectious material, blood, and secretions, and so the neonate may receive therapy without delay after birth.

**Acute exposure to blood that contains (or might contain) HBsAg.** For accidental percutaneous or permucosal exposure to blood that is known to contain or might contain HBsAg, the decision to provide prophylaxis must take into account several factors: (1) the hepatitis B vaccination status of the exposed person; (2) whether the source of blood is known or unknown; and (3) whether the HBsAg status of the source is known or unknown. Such exposures usually occur in persons who are candidates for hepatitis B vaccine; for any exposure in a person not previously vaccinated, hepatitis B vaccination is recommended.

The following outline and table summarize prophylaxis for percutaneous (needlestick or bite), ocular, or mucous-membrane exposure to blood according to the source of exposure and vaccination status of the exposed person (Table 5). For greatest effectiveness, passive prophylaxis with HBIG (or IG) should be given as soon as possible after exposure (its value beyond 7 days of exposure is unclear).

1. *Exposed person not previously vaccinated.* Hepatitis B vaccination should be considered the treatment of choice. Depending on the source of the exposure, HBsAg testing of the source and additional prophylaxis of the exposed person may be warranted (see below). Screening the exposed person for immunity should be considered if such screening is cost-effective (as discussed in preexposure prophylaxis) and if this will not delay treatment beyond 7 days.
   a. *Source known HBsAg-positive.* A single dose of HBIG (0.06 ml/kg) should be given as soon as possible after exposure and within 24 hours, if possible. The first dose of hepatitis B vaccine (20 $\mu$g) should be given intramuscularly at a separate site within 7 days of exposure, and the second and third doses given 1 month and 6 months later (Table 5).[†] If HBIG cannot be obtained, IG in an equivalent dosage (0.06 ml/kg) may provide some benefit.

[†]For persons who are not given hepatitis B vaccine, a second dose of HBIG should be given 1 month after the first dose.

**TABLE 4. Women for whom prenatal HBsAg screening is recommended**

1. Women of Asian, Pacific island, or Alaskan Eskimo descent, whether immigrant or U.S.-born.
2. Women born in Haiti or sub-Saharan Africa.
3. Women with histories of:
   a. Acute or chronic liver disease.
   b. Work or treatment in a hemodialysis unit.
   c. Work or residence in an institution for the mentally retarded.
   d. Rejection as a blood donor.
   e. Blood transfusion on repeated occasions.
   f. Frequent occupational exposure to blood in medico-dental settings.
   g. Household contact with an HBV carrier or hemodialysis patient.
   h. Multiple episodes of venereal diseases.
   i. Percutaneous use of illicit drugs.

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b. *Source known, HBsAg status unknown.* The following guidelines are suggested based on the relative probability that the source is HBsAg-positive and on the consequent risk of HBV transmission:

(1) *High risk that the source is HBsAg-positive, such as patients with a high risk of HBV carriage (Table 2) or patients with acute or chronic liver disease (serologically undiagnosed).* The exposed person should be given the first dose of hepatitis B vaccine (20 $\mu$g) within 1 week of exposure and vaccination completed as recommended. The source person should be tested for HBsAg. If positive, the exposed person should be given HBIG (0.06 ml/kg) if within 7 days of exposure.

(2) *Low risk that the source is positive for HBsAg.* The exposed person should be given the first dose of hepatitis B vaccine (20 $\mu$g) within 1 week of exposure and vaccination completed as recommended. Testing of the source person is not necessary.

c. *Source unknown.* The exposed person should be given the first dose of hepatitis B vaccine (20 $\mu$g) within 7 days of exposure and vaccination completed as recommended.

2. *Exposed person previously vaccinated against hepatitis B.* For percutaneous exposures to blood in persons who have previously received one or more doses of hepatitis B vaccine, the decision to provide additional prophylaxis will depend on the source of exposure and on whether the vaccinated person has developed anti-HBs following vaccination.

a. *Source known HBsAg-positive.* The exposed person should be tested for anti-HBs unless he/she has been tested within the last 12 months. If the exposed person has adequate[§] antibody, no additional treatment is indicated.

[§]Adequate antibody is 10 SRU or more by RIA or positive by EIA.

**TABLE 5. Recommendations for hepatitis B prophylaxis following percutaneous exposure**

| Source | Exposed person: Unvaccinated | Exposed person: Vaccinated |
|---|---|---|
| HBsAg-positive | 1. HBIG x 1 immediately* 2. Initiate HB vaccine[†] series. | 1. Test exposed person for anti-HBs.[§] 2. If inadequate antibody,[¶] HBIG (x1) immediately plus HB vaccine booster dose. |
| Known source | | |
| High-risk HBsAg-positive | 1. Initiate HB vaccine series 2. Test source for HBsAg. If positive, HBIG x 1. | 1. Test source for HBsAg only if exposed is vaccine nonresponder; if source is HBsAg-positive, give HBIG x 1 immediately plus HB vaccine booster dose |
| Low-risk HBsAg-positive | Initiate HB vaccine series. | Nothing required. |
| Unknown source | Initiate HB vaccine series. | Nothing required. |

*HBIG dose 0.06 ml/kg IM.

[†]HB vaccine dose 20 $\mu$g IM for adults; 10 $\mu$g IM for infants or children under 10 years of age. First dose within 1 week; second and third doses, 1 and 6 months later.

[§] See text for details.

[¶]Less than 10 SRU by RIA, negative by EIA.

(1) If the exposed person has not completed vaccination and has inadequate levels of antibody, one dose of HBIG (0.06 ml/kg) should be given immediately and vaccination completed as scheduled.

(2) If the exposed person has inadequate antibody on testing or has previously not responded to vaccine, one dose of HBIG should be given immediately and a booster dose of vaccine (1 ml or 20 $\mu$g) given at a different site.

(3) If the exposed person shows inadequate antibody on testing but is known to have had adequate antibody in the past, a booster dose of hepatitis B vaccine (1 ml or 20 $\mu$g) should be given.

b. *Source known, HBsAg status unknown.*

(1) *High risk that the source is HBsAg-positive.* Additional prophylaxis is necessary only if the exposed person is a known vaccine nonresponder. In this circumstance, the source should be tested for HBsAg and, if positive, the exposed person treated with one dose of HBIG (0.06 ml/kg) immediately and a booster dose of vaccine (1 ml or 20 $\mu$g) at a different site. In other circumstances, screening of the source for HBsAg and the exposed person for anti-HBs is not routinely recommended, because the actual risk of HBV infection is very low (less than 1 per 1,000).¶

(2) *Low risk that the source is HBsAg-positive.* The risk of HBV infection is minimal. Neither testing of the source for HBsAg, nor testing of the exposed person for anti-HBs, is recommended.

c. *Source unknown.* The risk of HBV infection is minimal. No treatment is indicated.

**Sexual contacts of persons with acute HBV infection**. Sexual contacts of HBsAg-positive persons are at increased risk of acquiring HBV infection, and HBIG has been shown to be 75% effective in preventing such infections (*31*). Because data are limited, the period after sexual exposure during which HBIG is effective is unknown, but extrapolation from other settings makes it unlikely that this period would exceed 14 days. Prescreening sexual partners for susceptibility before treatment is recommended if it does not delay treatment beyond 14 days after last exposure. Testing for anti-HBc is the most efficient prescreening test to use in this population group.

A single dose of HBIG (0.06 ml/kg) is recommended for susceptible individuals who have had sexual contact with an HBsAg-positive person, if HBIG can be given within 14 days of the last sexual contact, and for persons who will continue to have sexual contact with an individual with acute hepatitis B before loss of HBsAg in that individual. In exposures between heterosexuals, hepatitis B vaccination may be initiated at the same time as HBIG prophylaxis; such treatment may improve efficacy of postexposure treatment. However, since 90% of persons with acute HBV infection become HBsAg-negative within 15 weeks of diagnosis, the potential for repeated exposure to HBV is limited. Hepatitis B vaccine is, therefore, optional in initial treatment for such exposures. If vaccine is not given, a second dose of HBIG should be given if the index patient remains HBsAg-positive for 3 months after detection. If the index patient is a known carrier or remains positive for 6 months, hepatitis B vaccine should be offered to regular sexual contacts. For exposures among homosexual men, the hepatitis B vaccine series should be initiated at the time HBIG is given, since hepatitis B vaccine is recommended for all susceptible homosexual men. Additional doses of HBIG are unnecessary if vaccine is given. IG

¶Estimated by multiplying the risk of vaccine nonresponse in the exposed person (.10) by the risk of the needle source being HBsAg-positive (.05) by the risk of HBV infection in a susceptible person having an HBsAg-positive needle-stick injury (.20).

is an alternative to HBIG when it is not possible to obtain HBIG.

**Household contacts of persons with acute HBV infection**. Prophylaxis for other household contacts of persons with acute HBV infection is not indicated unless they have had identifiable blood exposure to the index case, such as by sharing toothbrushes or razors. Such exposures should be treated similarly to sexual exposures. If the index patient becomes a hepatitis B carrier, all household contacts should be given hepatitis B vaccine.

**DELTA HEPATITIS**

The delta virus (also known as hepatitis D virus [HDV] by some investigators) is a defective virus that may only cause infection in the presence of active HBV infection. The delta virus has been characterized as a particle of 35-37 nm in size, consisting of RNA (mw 500,000) as genetic material and an internal protein antigen (delta-antigen), coated with HBsAg as the surface protein (*3*). Infection may occur as either coinfection with hepatitis B or superinfection of a hepatitis B carrier, each of which usually cause an episode of acute hepatitis. Coinfection usually resolves, while superinfection frequently causes chronic delta infection and chronic active hepatitis. Both types of infection may cause fulminant hepatitis.

Delta infection may be diagnosed by detection of delta-antigen in serum during early infection and by the appearance of delta antibody during or after infection. Routes of delta transmission appear to be similar to those of hepatitis B. In the United States, delta infection occurs most commonly among persons at high risk of acquiring HBV infection, such as drug addicts and hemophilia patients.

A test for detection of delta antibody is expected to be commercially available soon. Other tests (delta antigen, IgM anti-delta) are available only in research laboratories.

Since the delta virus is dependent on hepatitis B for replication, prevention of hepatitis B infection, either preexposure or postexposure, will suffice to prevent delta infection in a person susceptible to hepatitis B. Known episodes of perinatal, sexual, or percutaneous exposure to sera or persons positive for both HBV and delta virus should be treated exactly as such exposures to hepatitis B alone.

Persons who are HBsAg carriers are at risk of delta infection, especially if they participate in activities that put them at high risk of repeated exposure to hepatitis B (parenteral drug abuse, homosexuality). However, at present there are no products available that might prevent delta infection in HBsAg carriers either before or after exposure.

**NON-A, NON-B HEPATITIS**

**United States**. Non-A, non-B hepatitis that presently occurs in the United States has epidemiologic characteristics similar to those of hepatitis B, occurring most commonly following blood transfusion and parenteral drug abuse. Multiple episodes of non-A, non-B hepatitis have been observed in the same individuals and may be due to different agents. Chronic hepatitis following acute non-A, non-B hepatitis infection varies in frequency from 20% to 70%. Experimental studies in chimpanzees have confirmed the existence of a carrier state, which may be present in up to 8% of the population.

Although several studies have attempted to assess the value of prophylaxis with IG against non-A, non-B hepatitis, the results have been equivocal, and no specific recommendations can be made (*35,36*). However, for persons with percutaneous exposure to blood from a patient with non-A, non-B hepatitis, it may be reasonable to administer IG (0.06 ml/kg) as soon as possible after exposure.

**Epidemic (fecal-oral) non-A, non-B hepatitis**. In recent years, epidemics of non-A, non-B hepatitis spread by water or close personal contact have been reported from several areas of Southeast Asia (Indian subcontinent, Burma) and north Africa (*2*). Such epidemics generally

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affect adults and cause unusually high mortality in pregnant women. The disease has been transmitted to experimental animals, and candidate viruses have been identified; however, no serologic tests have yet been developed (*37*).

Epidemic non-A, non-B hepatitis has not been recognized in the United States or western Europe, and it is unknown whether the causative agent is present in these areas.

Travelers to areas having epidemic non-A, non-B hepatitis may be at some risk of acquiring this disease by close contact or by contaminated food or water. The value of IG in preventing this infection is unknown. The best prevention of infection is to avoid potentially contaminated food or water, as with hepatitis A and other enteric infections.

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CENTERS FOR DISEASE CONTROL

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*Recommendations of the Immunization Practices Advisory Committee*

## Update on Hepatitis B Prevention

### INTRODUCTION

Hepatitis B virus (HBV) infection is a major cause of acute and chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma in the United States and worldwide. Since 1982, a safe and effective hepatitis B (HB) vaccine manufactured from human plasma has been available in the United States. This vaccine has been recommended as preexposure prophylaxis for persons at high or moderate risk of HBV infection (*1*). In addition, the combination of HB vaccine and hepatitis B immunoglobulin (HBIG) has been recommended for postexposure prophylaxis in susceptible persons who have perinatal or needle-stick exposure to known HBV-positive persons or their blood.

This statement provides an update on HB vaccine usage and on its impact on disease incidence in the 5 years following its licensure. In addition, it provides both recommendations for using a new HB vaccine produced in yeast by recombinant DNA technology and an assessment of the need for HB vaccine booster doses for persons who have received the initial three-dose regimen. Basic recommendations on preexposure and postexposure usage of HB vaccine and on prevaccination serologic testing for susceptibility to hepatitis B are unchanged. Previous recommendations should be consulted for a complete discussion of the usage of HB vaccine (*1*).

### PLASMA-DERIVED HB VACCINE

#### Patterns of Usage to Date

Since the plasma-derived HB vaccine became available in June 1982, 4,400,000 doses have been distributed in the United States, and an estimated 1,400,000 persons have completed the three-dose series (Merck Sharp & Dohme, unpublished data). During this 5-year period, vaccination programs and overall vaccine usage have focused primarily on three risk groups – persons who work in health-care professions and have exposure to blood, staff and clients of institutions for the developmentally disabled, and staff and patients in hemodialysis units. Although no precise figures are available, it is estimated that more than 85% of distributed vaccine has been used for these groups.

Development of vaccination programs for health-care workers has progressed steadily since vaccine licensure. Several surveys of hospitals in 1985 showed that between 49% and 68% of hospitals had established HB vaccination programs and that the number has increased steadily each year (CDC, unpublished data). Large hospitals (>500 beds) were most likely to establish programs (90%). However, by June 1985, 60% of hospitals with fewer than 100 beds also had begun vaccination programs. In 75% of the programs, vaccination was recommended for high-risk health-care workers (as defined by the hospital), and, in 77%, the hospital paid for these vaccinations. In addition, 70% of states had established programs for vaccinating health-care workers under state jurisdiction (CDC, unpublished data).

In spite of these programs, the actual use of vaccine in high-risk health-care professions has been modest. One statewide survey showed that, in hospitals with HB vaccine programs, only 36% of persons at high risk had actually received vaccine (CDC, unpublished data). In one survey in three large cities, only 24% of physicians had received vaccine (CDC, unpublished data). National surveys have shown higher rates of vaccination among dentists (44% in early 1986) and hemodialysis staff (an estimated 44% in 1985); however, even these rates fall well short of optimal coverage (CDC, unpublished data).

Development of vaccination programs has also progressed for several other groups at high risk of HBV infection. By mid-1985, 94% of states had established vaccination programs for the developmentally disabled in institutions under state jurisdiction, and 75% had programs for staff of such facilities (CDC, unpublished data). By 1986, an estimated 27% of the developmentally disabled had received HB vaccine (Merck Sharp & Dohme, unpublished data). In addition, wide-scale programs directed at vaccinating all susceptible persons were established in 1981 for Alaskan Natives and in 1985 for the population of American Samoa.

Nevertheless, there has been little progress in developing vaccination programs for other major risk groups, including parenteral drug abusers, homosexual men, and heterosexually active persons with multiple sexual partners. Few states have established programs for offering vaccine to any of these groups, and private usage of vaccine among these groups is believed to be limited.

**Impact on Disease Incidence**

The incidence of reported hepatitis B has increased steadily over the last decade. Hepatitis B is now the most commonly reported type of hepatitis in the United States. In 1978, 15,000 cases of clinical hepatitis B were reported to CDC, for an incidence rate of 6.9/100,000 population. At that time, CDC estimated that there were actually 200,000 persons with HBV infection and that 50,000 of these had clinically confirmed cases with jaundice. The incidence rate of reported disease increased 33%, to 9.2/100,000, in 1981, the year prior to vaccine availability. It continued to increase during the initial 4 years of vaccine availability, reaching a rate of 11.5/100,000 in 1985 (*2*). Based on a comparison with the overall infection rate estimated in 1978, the incidence of HBV infection in the United States is now estimated at over 300,000 cases per year.

The apparent lack of impact of HB vaccine on the incidence of hepatitis B is attributable to several factors. First, the majority of acute hepatitis B cases now occur in three groups: homosexual men, parenteral drug abusers, and persons acquiring disease through heterosexual exposure (*3*). None of these groups is being reached effectively by current HB vaccine programs. In contrast, fewer than 10% of cases occur in health-care workers, the institutionalized developmentally disabled, and other groups currently accounting for the bulk of vaccine usage. Finally, up to 30% of

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patients deny any of the recognized risk factors, even after careful questioning. No effective strategy has been devised to prevent disease among this group, although some are probably undisclosed members of the three major risk groups.

A reduction in the incidence of hepatitis B can be expected only if significant proportions of persons at high risk receive vaccine. Increased efforts are needed to develop programs to vaccinate persons in all high-risk groups and to increase compliance among those who are susceptible in areas where programs are established. To have any effect on the incidence of hepatitis B, use of HB vaccine in the United States must extend beyond the current groups of recipients.

## NEW RECOMBINANT DNA HB VACCINE

### Formulation

In July 1986, a new, genetically engineered HB vaccine (Recombivax HB®; Merck Sharp & Dohme) was licensed by the U.S. Food and Drug Administration. This vaccine, as formulated, has an immunogenicity comparable to that of the currently available plasma-derived vaccine (Heptavax B®; Merck Sharp & Dohme). The two vaccines are also comparably effective when given with HBIG to prevent perinatal HBV transmission. The new vaccine provides an alternative to the plasma-derived HB vaccine for almost all groups at risk of HBV infection.

The recombinant vaccine is produced by *Saccharomyces cerevisiae* (common baker's yeast) into which a plasmid containing the gene for the Hepatitis B surface antigen (HBsAg) subtype adw has been inserted (*4*). HBsAg is harvested by lysing the yeast cells and is separated from yeast components by hydrophobic interaction and size-exclusion chromatography. The purified HBsAg protein undergoes sterile filtration and treatment with formalin prior to packaging. The vaccine is packaged to contain 10μg HBsAg protein per ml, adsorbed with 0.5 mg/ml aluminum hydroxide; a 1:20,000 concentration of thimerosal is added as a preservative.

The recombinant HBsAg takes the form of 17-25 nm spherical particles, similar in appearance to human plasma-derived HBsAg. The recombinant particles differ in that the HBsAg is not glycosylated, whereas up to 25% of plasma-derived HBsAg is glycosylated. The vaccine contains more than 95% HBsAg protein. Yeast-derived protein can constitute up to 4% of the final product, but no yeast DNA is detectable in the vaccine.

### Immunogenicity and Efficacy

The immunogenicity of the recombinant HB vaccine is comparable to that of the plasma-derived product (*5*). When given in a three-dose series (10μg per dose), recombinant HB vaccine induces protective antibodies (anti-HBs*) in over 95% of healthy adults 20-39 years of age. Studies comparing antibody responses of healthy adults show equal rates of seroconversion following the three doses of either the recombinant vaccine (10μg per dose) or the plasma-derived vaccine (20μg per dose). However, the geometric mean titers (GMT) of antibodies developed by recipients of the recombinant vaccine have ranged from equal to to 30% as high as those developed by recipients of the plasma-derived vaccine. The recombinant vaccine, like the plasma-derived vaccine, produces a somewhat lower antibody response in older adults than in younger adults (*5*).

In studies using three 5-μg doses of recombinant vaccine for children<12 years of age, over 99% of the recipients have developed protective levels of antibodies. Hemodialysis patients develop a poorer response to the recombinant vaccine than do

*Greater than 10 milli-International Units (mIU)/ml of anti-HBs, approximately equal to 10 sample ratio units by radioimmunoassay or positive by enzyme immunoassay.

healthy adults. For example, in one study using three 40-μg doses of recombinant HB vaccine, only 64% of vaccine recipients developed protective levels of antibodies.

The recombinant HB vaccine has been shown to prevent HBV infection of vaccinated chimpanzees challenged intravenously with HBV of either adw or ayr subtypes. In studies of infants born to HBsAg- and HBeAg-positive mothers, the combination of HBIG (0.5 cc at birth) and recombinant HB vaccine (5μg in each of three doses) protected 94% of infants from developing the chronic carrier state, an efficacy equalling that of HBIG plus plasma-derived HB vaccine (*6*). The simultaneous administration of HBIG did not interfere with induction of anti-HBs antibody response by the recombinant HB vaccine.

There have been no large-scale efficacy trials of recombinant vaccine in adults. Nevertheless, the immunogenicity studies, the challenge studies using chimpanzees, and the efficacy trials of the HB vaccine and HBIG in infants born to mothers who are carriers of HBV strongly suggest that the efficacy of recombinant HB vaccine in adults is comparable to that of the plasma-derived product.

**Safety**

Because only the portion of the HBV viral genome that codes for the surface coat of the virus (HBsAg) is present in the recombinant yeast cells, no potentially infectious viral DNA or complete viral particles can be produced. No human or animal plasma or other blood derivative is used in the preparation of recombinant HB vaccine.

During prelicensure trials, approximately 4,500 persons received at least one dose, and 2,700 persons completed the vaccine series (*5*). Reported side effects were similar in extent and variety to those following administration of the plasma-derived vaccine. Seventeen percent of those vaccinated experienced soreness at the injection site, and 15% experienced mild systemic symptoms (fever, headache, fatigue, and nausea). To date, no severe side effects have been observed, nor have significant allergic reactions been reported. Although yeast-derived proteins may constitute up to 4% of the protein in the vaccine, no adverse reactions that could be related to changes in titers of antibodies to yeast-derived antigens occurred during clinical trials.

Early concerns about safety of plasma-derived HB vaccine, especially the concern that infectious agents such as human immunodeficiency virus (HIV) present in donor plasma pools might contaminate the final product, have proven to be unfounded (*7*). There are no data to indicate that the recombinant vaccine is potentially or actually safer than the currently licensed plasma-derived product.

**Dosage and Schedule**

The recombinant HB vaccine is given in a series of three doses over a 6-month period. The second dose is administered 1 month after the first, and the third dose, 5 months after the second. For normal adults and children>10 years of age, the recommended dose is 10μg (1 ml) intramuscularly in each of the three inoculations. Children<11 years of age should receive a 5-μg dose (0.5 ml) by the same schedule. Newborns of mothers who are carriers of HBsAg should receive the three-dose series (5μg per dose) by the same schedule; however, the first dose, which is given at birth, should be combined with a single dose of HBIG (0.5 ml) given intramuscularly at another site.

The recommended dose of recombinant HB vaccine for hemodialysis patients or other immunosuppressed persons is 40μg, which is identical to the dose of plasma-derived vaccine recommended for these groups. A specially formulated preparation

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(40μg HBsAg protein/ml adsorbed with 0.5 mg aluminum hydroxide) is being developed for these patients. At present, it is not advisable to administer the standard formulation of recombinant HB vaccine to these patients because this would require a large volume (4.0 cc), which is inconvenient for injection in the deltoid muscle, and would contain more aluminum hydroxide (2.0 mg) than currently recommended as an adjuvant in vaccines (1.25 mg per dose). Only plasma-derived vaccine should be used for these patients.

As with plasma-derived vaccine, recombinant HB vaccine should only be given to older children and adults in the deltoid muscle and to neonates or infants in the anterolateral thigh muscle. The vaccine should be stored at 2 C to 6 C (36 F to 43 F) and *should not be frozen*; freezing destroys the potency of this vaccine.

The response to vaccination by the standard schedule using one or two doses of plasma-derived vaccine followed by the remaining doses of recombinant vaccine has not been studied. However, because the immunogenicities of the two vaccines are similar, it is likely that the response will be comparable to that induced by three doses of either vaccine alone. The response to revaccination with the recombinant vaccine following nonresponse to an initial series of plasma vaccine has not been evaluated.

**Indications for Use**

The indications for use of the recombinant HB vaccine are identical to those for the plasma-derived product, except that the present formulation of the recombinant HB vaccine should not be used for hemodialysis patients or other immunosuppressed persons (Table 1) (*1*). For other groups, including persons with Down's syndrome, there are no data indicating that the recombinant HB vaccine is either superior or inferior to the plasma-derived HB vaccine for any preexposure or postexposure indication.

**Precautions**

The recombinant HB vaccine contains only noninfectious HBsAg particles; therefore, vaccination of a pregnant woman should entail no risk to either the woman or the fetus. Furthermore, HBV infection in a pregnant woman can result in severe disease for the mother and chronic infection of the newborn. Pregnancy should not be

**TABLE 1. Persons for whom hepatitis B vaccine is recommended or should be considered***

**Preexposure**

Persons for whom vaccine is recommended:

- Health-care workers having blood or needle-stick exposures
- Clients and staff of institutions for the developmentally disabled
- Hemodialysis patients
- Homosexually active men
- Users of illicit injectable drugs
- Recipients of certain blood products
- Household members and sexual contacts of HBV carriers
- Special high-risk populations

Persons for whom vaccine should be considered:

- Inmates of long-term correctional facilities
- Heterosexually active persons with multiple sexual partners
- International travelers to HBV endemic areas

**Postexposure**

- Infants born to HBV positive mothers
- Health-care workers having needle-stick exposures to human blood

*Detailed information on recommendations for HB vaccination is available (*1*).

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considered a contraindication for women in high-risk groups who are eligible to receive this vaccine.

**NEED FOR VACCINE BOOSTER DOSES**

**Long-Term Protection by Plasma-Derived HB Vaccine**

In short-term efficacy studies, the plasma-derived HB vaccine provided protection against HBV infection for 85%-95% of vaccine recipients, including virtually all those who developed adequate levels of antibodies (see footnote on pg. 355) (*8,9*). A recent evaluation of the long-term protection afforded by this vaccine (>5 years) provides a basis for recommendations concerning the need for booster doses in previously vaccinated persons (*10*).

Currently available data indicate that vaccine-induced antibody levels decline significantly (*10*). Antibody may decrease to low levels for 30%-40% of vaccinated adults who initially develop adequate levels of antibody during the 5 years after vaccination, and it may become undetectable in 10%-15% of them. The duration of antibody persistence is directly related to the peak level achieved after the third dose of vaccine (*11*). The longer persistence of detectable levels of antibody observed in children and young adults (<20 years of age) is consistent with the higher peak response in these age groups.

Studies of the licensed plasma-derived HB vaccine in adults have demonstrated that, in spite of declining levels of antibody, protection against clinical (or viremic) HBV infection persists for >5 years (*10*). Although the risks of HBV infection appear to increase as antibody levels become low or undetectable, the resultant infections are almost always innocuous and do not cause detectable viremia, liver inflammation, or clinical illness. These infections are detected by serologic evidence of an increase of anti-HBs levels associated with the appearance of antibody to the hepatitis B core antigen (anti-HBc). To date, only one transient viremic infection has been recognized in a vaccine responder within 72 months after vaccination. This infection produced mild alanine aminotransferase elevation, but no clinical illness (*10*). Thus, among adults who have responded to the vaccine, protection against clinically significant HBV infection appears to outlast the presence of detectable anti-HBs and can persist for ≥2 years among vaccine recipients whose antibodies have declined to low or undetectable levels.

For infants born to mothers who are carriers of HBV, there are insufficient data to assess duration of antibody persistence and protection against clinically significant HBV infection with the U.S. plasma-derived vaccine. One study, in a developing country (Senegal) and using a different plasma-derived HB vaccine, has demonstrated that protection against viremic HBV infection can decline within 6 years in infants vaccinated between 6 months and 2 years of age (*12*). Firm data on the duration of protection among infants receiving the vaccines licensed in the United States will be necessary before recommendations on booster doses can be made for this group.

**Postvaccination Testing of Response to Vaccine**

When properly administered, HB vaccine produces anti-HBs in more than 90% of healthy persons. Testing for immunity following vaccination has been recommended only for persons in whom suboptimal response to vaccine is anticipated, including persons who received vaccine in the buttock or persons, such as hemodialysis patients, whose subsequent management depends on knowing their immune status (*1*). Revaccination, which has produced adequate antibody in only 30%-50% of persons who have not responded to primary vaccination in the deltoid, is not routinely recommended (*1,10*).

Vaccine program coordinators in hospitals may decide to test vaccine recipients serologically to assess their antibody responses, even though such postvaccination testing is not routinely recommended. Persons electing to do postvaccination testing should be aware of potential difficulties in interpreting the results. Serologic testing within 6 months of completing the primary series will differentiate persons who respond to vaccine from those who fail to respond. However, the results of testing undertaken more than 6 months after completion of the primary series are more difficult to interpret. A vaccine recipient who is negative for anti-HBs between 1 and 5 years after vaccination can be 1) a primary nonresponder who remains susceptible to hepatitis B or 2) a vaccine responder whose antibody levels have decreased below detectability but who is still protected against clinical HBV disease (*10*).

There is no need for routine anti-HBs testing 1 to 5 years after vaccination unless there has been a decision to provide booster doses for persons who are anti-HBs negative. This strategy is medically acceptable, but costly, and will prevent few additional cases of disease because of the excellent long-term protection already provided by the primary series of vaccine.

**Recommendations for Booster Doses**

***Adults and children with normal immune status.*** For adults and children with normal immune status, the antibody response to properly administered vaccine is excellent, and protection lasts for at least 5 years. *Booster doses of vaccine are not routinely recommended, nor is routine serologic testing to assess antibody levels in vaccine recipients necessary during this period.* The possible need for booster doses after longer intervals will be assessed as additional information becomes available.

***Hemodialysis patients.*** For hemodialysis patients, in whom vaccine-induced protection is less complete and may persist only as long as antibody levels remain above 10 mIU/ml, the need for booster doses should be assessed by semiannual antibody testing (*13*). Booster doses should be given when antibody levels decline below 10 mIU/ml.

**Postexposure Prophylaxis of Persons Exposed to HBsAg Positive Needle Sticks**

In vaccinated persons who experience percutaneous or needle exposure to HBsAg-positive blood, serologic testing to assess immune status is recommended unless testing within the previous 12 months has indicated adequate levels of antibody. If the exposed person is tested and found to have an inadequate antibody level, treatment with HBIG and/or a booster dose of vaccine is indicated, depending on whether vaccination has been completed and whether the person is known to have previously responded to HB vaccine. Detailed recommendations on prophylaxis in this situation are provided in the previous recommendations for HB vaccine (*1*).

**Dosage**

When indicated, HB vaccine recipients can be given booster doses of either plasma-derived or recombinant HB vaccine. Booster doses of either vaccine induce prompt anamnestic responses in over 90% of persons who initially respond to vaccine but subsequently lose detectable antibody (*14,15*). The booster dose for normal adults is 20μg of plasma-derived vaccine or 10μg of recombinant vaccine. For newborns and children<10 years of age, the dose is half that recommended for adults. For hemodialysis patients, a dose of 40μg of plasma-derived vaccine is recommended; a formulation of recombinant HB vaccine is not yet available for this

*ACIP: Hepatitis B — Continued*

group. Vaccine should be given in the deltoid muscle. Buttock injection does not induce adequate levels of antibody.

**Precautions**

Reported adverse effects following booster doses have been limited to soreness at the injection site. Data are not available on the safety of the vaccine for the developing fetus, but there should be no risk because both plasma-derived and recombinant HB vaccines are inactivated and do not contain live virus particles. Booster doses need not be withheld from pregnant women who are at ongoing risk of HBV infection.

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OTHER MEDICAL DEPARTMENT RESPONSIBILITIES, INFORMATION, AND SOURCES OF CONSULTATION FOR THE PREVENTION AND CONTROL OF VIRAL HEPATITIS AND MANAGEMENT OF HEPATITIS B VIRUS (HBV) CARRIERS

1. Mass Prophylaxis. Mass prophylaxis with immune globulin (IG) is seldom indicated. In those instances in which IG is administered for prevention of HAV, it should be remembered that a primary consideration is the relative cost of administering the IG versus the cost or risk of having personnel come down with HAV, generally a mild disease with few serious consequences in terms of morbidity or mortality. Consultation with the area NAVENPVNTMEDU is highly recommended prior to any decision to administer mass IG prophylaxis.

2. Preexposure Prophylaxis

a. HAV Preexposure Prophylaxis. Preexposure IG prophylaxis for HAV is less important than education of Navy health care beneficiaries on proper hygiene and sanitary measures to prevent enteric infections. (A

(1) Personnel Ashore. Preexposure IG prophylaxis for HAV is not recommended for personnel traveling to HAV-endemic areas using ordinary tourist routes and staying less than 2 months. Personnel ashore in highly HAV-endemic areas or in HAV-endemic areas longer than 2 months with significant HAV exposure likely, however, should be administered preexposure IG prophylaxis. Navy and Marine Corps personnel serving at overseas diplomatic missions or other non-CONUS activities in highly HAV-endemic areas under the cognizance of the Department of State are authorized to receive prophylactic IG under this directive. Navy or Marine Corps personnel operating under joint services command may receive IG if recommended by the staff medical officer advising the joint commanders. Current information regarding highly HAV-endemic areas may be obtained from the area NAVENPVNTMEDU. (R

(2) Personnel Afloat. During fleet operations in highly HAV-endemic areas, the staff medical officer should consider administering IG prophylaxis to key personnel aboard ship (e.g., commanding officer, executive officer, navigator, etc.). However, IG should not be given routinely to all shipboard personnel going ashore in a leave or liberty status or to debarking Marine Corps personnel in HAV-endemic areas unless directed by the applicable force medical officer or recommended by the area NAVENPVNTMEDU.

(3) Dependents and Others. Voluntary IG prophylaxis for dependents and other civilians under Navy or Marine Corps

cognizance in highly HAV-endemic areas may be provided. Criteria for recommendations and dosages are per enclosure (1).

(4) IG Dosages. For adult personnel with significant probable HAV exposure in a highly HAV-endemic area for up to 2 months, a single intramuscular IG injection of 0.02 - 0.04 ml/kg (more easily standardized as 2 ml for an average-weight adult) is recommended. Persons in highly HAV-endemic areas and with significant exposure probable over longer periods of time should receive an intramuscular IG injection in a dosage of 0.06 ml/kg (maximum dosage of 5 ml for an adult) every 5 months.

b. HBV Preexposure Prophylaxis. HBV vaccine must be provided for individuals covered under this instruction, including active duty personnel, dependents, appropriated fund and nonappropriated fund employees and volunteers, who are in high risk occupational situations characterized by frequent potential contact with human blood, blood products, or other body fluids. HBV vaccine should also be provided for persons under Navy or Marine Corps authority who are considered at high risk due to circumstances of household contact, deployment to highly HBV-endemic areas, or sexual exposure. The following information must be used in developing and implementing local guidelines for HBV vaccine administration. Further guidance on risk assessment and susceptibility screening for health care workers and other high risk groups, and information on highly HBV-endemic areas are contained in enclosures (1) and (2) or can be obtained from the area NAVENPVNTMEDU.

(1) Health Care Workers. In health care and emergency medical response settings, persons who handle potentially contaminated blood or body fluids are at high occupational risk for acquiring HBV infection. Contingency considerations may make it necessary to administer HBV vaccine to other assigned health care personnel. The following Navy Medical Department personnel and some other Navy personnel or employees must be immunized with HBV vaccine:

(a) Medical Department personnel in operational settings or assigned to deployable medical units including fleet hospitals and mobile medical augmentation readiness teams (MMARTs).

(b) Navy medical students at the Uniformed Services University of the Health Sciences and Navy students on various Health Professions Scholarship Programs during periods of ACDUTRA, or during clerkships at Navy medical treatment facilities, as practicable. Administer the first two doses during the first available ACDUTRA or clinical clerkship, and the third dose during the next period of active duty or clerkship.

(c) All interns and residents in Navy medical and dental treatment facilities.

(d) Operating room staff, including technicians.

(e) Surgeons (general and all subspecialties).

(f) Pathologists and their technical assistants.

(g) Persons who perform phlebotomies.

(h) Persons who frequently insert intravenous or intra-arterial lines.

(i) Oncology unit staff, including technicians.

(j) Emergency room staff, including technicians, ambulance attendants, and other "first responders" (i.e., firemen, security personnel, etc.). (A

(k) Hemodialysis unit staff, including technicians.

(l) Laboratory personnel, including medical technologists and technicians.

(m) Blood bank personnel.

(n) Dentists, oral surgeons, dental hygienists, and technicians.

(o) Labor deck and delivery room staff, including technicians.

(p) Some laundry and housekeeping staff.

(q) Other Navy Medical Department personnel as may be directed or appropriate.

(2) Occupational, Berthing, and Household Contacts. Over time (e.g., 6 months or greater), some household contacts of HBV carriers are at high risk of acquiring HBV infection. When HBV carriers are identified, they must be notified of their status and any household contacts who are known to be susceptible should be immunized with HBV vaccine. This may occasionally include some susceptible persons who share berthing compartments or cramped work spaces with HBV carriers aboard ships. Consult the cognizant NAVENPVNTMEDU for guidance in such cases. See paragraph 4. (R

(3) Deployment to Highly HBV-endemic Areas. Administer at least two doses of HBV vaccine, prior to departure, to all personnel ordered to duty as embassy security guards in highly HBV-endemic areas. Other Navy and Marine Corps personnel and other persons under Navy or Marine Corps authority deployed to (R

or stationed for 6 months or longer in highly HBV-endemic areas are at increased risk of acquiring HBV infection. As such, HBV infection is considered an occupational hazard for Navy and Marine Corps personnel. Therefore, all personnel stationed for 6 months or longer in, or deploying to, highly HBV-endemic areas should be offered immunization with HBV vaccine. Persons being transferred to deployable units in such settings should be offered at least the first dose of HBV vaccine, preferably the first two doses, prior to transfer.

(4) Sexual Contacts. Susceptible persons who have sexual contact with HBV-positive persons are at high risk of contracting infection. See enclosures (1) and (2) for guidance.

(5) Federal Civilian Employees. Federal civilian employees, including volunteers, working in Navy medical facilities with jobs listed in paragraph 2b(1), or who are assigned to duty in highly HBV-endemic areas, must be provided HBV vaccine without charge as a funded occupational health service per reference (e).

(6) Dosages and Routes of Administration. Administer HBV vaccine as described in enclosures (1) and (2) or in the manufacturer's package insert. The Commander, Naval Medical Command may direct alternative schedules or routes of administration of HBV vaccine to be followed for military personnel such as intradermal use of formalin-inactivated HBV vaccine. Booster doses are not currently recommended as a standard practice; however, follow ACIP recommendations or the manufacturer's package insert if boosters become standard recommended procedure.

(7) Susceptibility Screening. Persons being considered for HBV vaccine may first be tested for the presence of HBV markers per enclosures (1) and (2). Persons positive for surface antibody need not receive HBV vaccine.

3. Postexposure Prophylaxis. In every case of suspected or confirmed hepatitis, the type should be serologically determined if possible. The patient's contacts must be rapidly identified and prophylaxis given if indicated. Generally, administration of prophylaxis to other than the few closest contacts is unnecessary. In a given situation, if more than 10 people are being considered for prophylaxis, consultation with the cognizant NAVENPVNTMEDU is strongly recommended. If the hepatitis type cannot be determined expeditiously (i.e., at sea or other isolated sites), approach the public health aspects of the case as if dealing with HAV and administer IG as described below to the few closest contacts without delay. On the other hand, approach the case clinically as if dealing with both HAV and HBV, with minimal enteric precautions as described below plus needle and blood precautions in the health

care setting per enclosures (1) and (2). Blood samples should be drawn from the patient and the sera frozen and retained for serologic testing when available. Scrupulous hand washing by the patient must be enforced. Otherwise, the person can eat meals with others and do daily activities as the clinical condition permits (with the exception of foodhandlers who must not handle food until 14 days have passed after the onset of their symptoms).

a. HAV Exposure

(1) Transmission. HAV is transmitted per rectum from infected individuals who have poor personal hygiene (hands contaminated after defecation but not washed). This occurs frequently among young children. HAV is also often transmitted when hands are contaminated cleaning feces from or changing diapers of infected young children. (HAV is often subclinical among young children.) Spread of infection results when contaminated hands come into direct or indirect contact with the mouths of other people who happen to be susceptible. In household settings, this can occur when contaminated hands are used to handle food. In highly HAV-endemic areas, the virus is often acquired by drinking contaminated water, using contaminated ice, consuming food obtained from street vendors, or eating other "high risk" food items such as raw fruits and vegetables. HAV is not transmitted through saliva; thus, kissing or sharing coffee cups or utensils, etc., are not considered risk factors. When conducting case or outbreak investigations, the first step is to determine whether or not the index case usually practiced good personal hygiene, washing their hands thoroughly after defecation. A useful clue, particularly among food handlers, is to examine the person's fingernails. If there is considerable dirt and grime under them, and which appears to have been there for some time, the odds are greater that the person did not practice good personal hygiene. If good hygiene was used, risk of transmission of HAV to contacts can be assumed to have been minimal. (R

(2) Public Health Rationale. Shedding or excretion of HAV from the intestinal tract of an infected individual generally parallels the development of the disease (replication of the virus during the incubation period) in the patient and correlates with "infectivity" of the patient. It may be easiest to remember that the epidemiology and management of HAV cases is based on the number "14" (see enclosure (5)). (A

(a) Intimate contacts of the primary HAV case who were enterically exposed during the 14 days prior to the case's developing symptoms can be considered at risk of having become infected. This 14 day period prior to the appearance of jaundice is the time of peak HAV replication or excretion.

(b) An exposed contact should receive IG as soon as practicable within 14 days of the actual exposure. The recommended postexposure dosage is a single intramuscular injection of 0.02 - 0.04 ml/kg (2 ml for an "average size" man or woman). If the contact is located more than 14 days after his or her first probable exposure, then administration of IG will likely be of little value.

(c) Persons receiving postexposure IG must be informed that IG prophylaxis is at best only 80 to 90 percent effective in preventing clinical HAV in exposed individuals. Even if clinical illness is prevented, such people can have subclinical HAV with enteric shedding of the virus. Therefore, such persons must neither ignore nor become careless in observing meticulous hand washing after defecation to prevent transmission of HAV among their contacts.

(d) After the onset of jaundice or other symptoms, HAV patients are noninfectious after 7 to 14 days have passed. Scrupulous hand washing after defecation must be enforced.

(3) Food Handlers. Some situations involving HAV infections in certain types of food handlers may pose an exception and necessitate consideration of mass prophylaxis. Sanitary food handling practices, if followed judiciously as described in reference (b), constitute safeguards which diminish the risk of HAV transmission from an infected food handler. However, breakdowns in sanitation among infected handlers of "high risk" food items (e.g., mishandling of salad vegetables; ungloved handling of dinner rolls or pastry after cooking, etc.), may necessitate consideration of mass prophylaxis for some patrons of the food service facility involved. HAV infection in a scullery worker or in other individuals who have merely handled kitchen utensils or served food via utensils does not pose a high risk to patrons of the food service facility. Mass IG prophylaxis of patrons in such situations is seldom indicated. Enclosure (4) should be consulted prior to making any decision to proceed with mass prophylaxis. Guidance from the cognizant NAVENPVNTMEDU is strongly advised in such situations.

(4) Day Care Centers. A number of recent HAV outbreaks among Navy and Marine Corps personnel have resulted from transmission via children in day care centers. Day care center personnel must be instructed on the dangers of fecal contamination and be required to wash their hands between each diaper change. Health standards for day care centers are described in reference (d).

b. HBV Exposure. General guidance for HBV postexposure prophylaxis is in enclosures (1) and (2). Manage such situations per these enclosures. See paragraph 4 below for special situations involving contacts of HBV carriers.

c. NANB Exposure. Guidance for NANB postexposure situations is in enclosure (1). In cases of recent known exposure to Epidemic (fecal-oral) NANB, contact the cognizant NAVENPVNTMEDU for further guidance. (R

d. Delta Hepatitis. See enclosure (1) and consult the area NAVENPVNTMEDU for guidance.

4. Management and Disposition Guidelines for HBV Carriers. Preventing misunderstanding and unreasonable management of HBsAg positive people is extremely important. An HBV carrier is an individual who is HBsAg positive at two points in time, at least 6 months apart. Active duty Navy or Marine Corps personnel who become HBV carriers, but who do not have evidence of chronic, persistent, or recurrent active hepatitis must not be restricted in any way from continued full active duty because of their HBV carrier status, provided the guidelines detailed below are observed as practicable. However, HBV carriers who do have evidence of chronic, persistent, or recurrent active hepatitis must be evaluated by a medical board. Decisions to retain such persons on active duty must be based on severity of symptoms, prognosis, and the needs of the naval service. Individuals who are known to be persistent HBV carriers must be disqualified from entering the Navy or Marine Corps unless a special waiver is granted by the Commander, Naval Medical Command. Medical Department representatives should implement the following guidelines for management of HBV carriers as practicable and as operational situations permit. (A

a. Clinical Management. HBV carriers with persistent symptoms or elevated hepatic enzyme levels and who are retained on active duty should be periodically evaluated by the medical officer following the case. Asymptomatic carriers should be seen annually by a medical officer for clinical evaluation, biochemical tests as needed, and specific serologic tests to determine the persistence of the carrier state.

b. Health Education. Inform HBV carriers about potential sequelae of the carrier state and the risk of HBV transmission to others. Emphasize transmission risks via blood and sexual contact. Educate HBV carriers not to share with other people razors, toothbrushes, or other items which may come into contact with blood or mucous membranes. HBV carriers who are women of childbearing age must be informed about the need for HBIG and HBV vaccine to prevent chronic HBV infection in their children.

c. Household and Other Intimate Contacts. Household and other intimate contacts of HBV carriers should be evaluated for susceptibility to HBV. Many long-time contacts of recently identified HBV carriers will be found to be already immune to HBV or (R at relatively low risk of acquiring HBV from the carrier. Transmission risks are greatest for the new, recent, or future sexual partners of those HBV carriers who are also HBeAg positive, but these situations are usually very difficult to identify on a timely basis. Nevertheless, all susceptible sexual or household contacts should receive HBV vaccine (see paragraphs 2b(2), 2b(3), and enclosure (2)).

d. Other Contacts. Other contacts of HBV carriers in schools, offices, those aboard ship who are not long-term working space associates, etc., are at minimal risk of acquiring HBV infection from the identified carrier. Accordingly, no specific precautions are generally indicated. In exceptional situations, such as mentally handicapped HBV carriers who exhibit aggressive behavior and are in close association with susceptible children (who often show similar behavior), consideration may be given to offering vaccine to such contacts.

e. Medical and Dental Health Care Personnel. Medical and dental health care personnel found to be HBsAg positive must not be restricted from patient contact, operative dentistry, or surgical activity solely on the basis of this serologic finding. Rather, they must be educated about the potential mechanisms of transmission so that appropriate efforts may be made to minimize any risk of transmission. Use of gloves must be emphasized. On rare occasions, hepatitis B has been transmitted in health care settings by HBsAg positive health care workers, but these have been exceptional cases involving a combination of factors that facilitate transmission: HBeAg positivity; a high degree of trauma to the patient that provides many possible entry points for the virus; and ready access of serous fluid from the HBV carrier to open tissue of a patient (as could occur with weeping dermatologic lesions or trauma to health care personnel during the course of work). If the latter circumstances are not present, transmission is unlikely to occur, even if the HBV carrier is HBeAg positive.

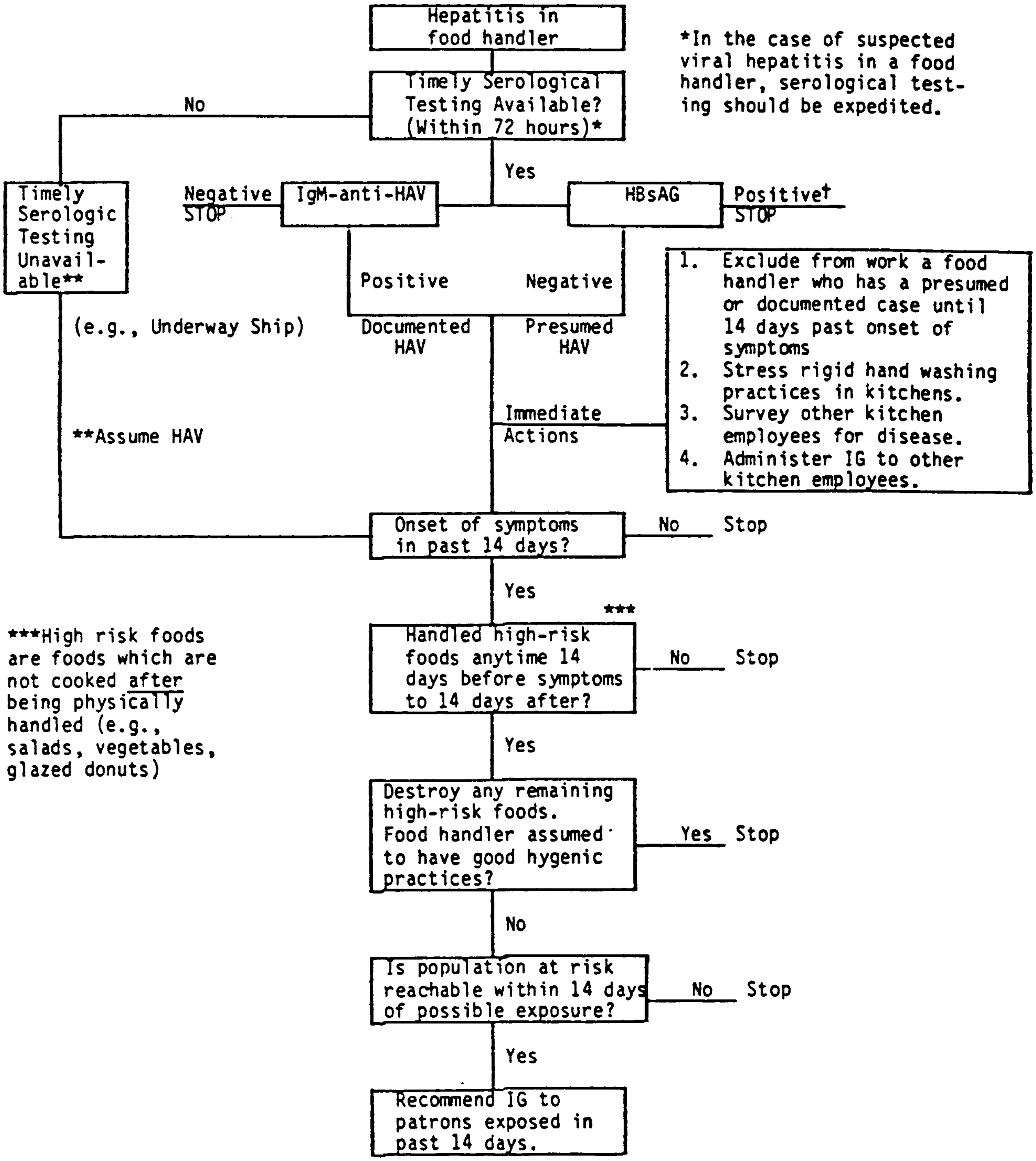
f. Food Handlers. Because HBV is not spread in a fecal-oral fashion, HBV carriers may work as food handlers.

5. Supplies

| Item | NSN |
|---|---|
| Immune Globulin (IG) | 6505-00-153-8278 |
| HBV Immune Globulin (HBIG) | 6505-01-052-6862 |
| HBV Vaccine | 6505-00-139-5000, acquisition code L |

6. Emergency Procurement in Operational Situations. Operational commands requiring emergency procurement of IG or HBIG should contact the appropriate force medical officer. Emergency procurement of IG or HBIG can be made by submitting a priority message MILSTRIP requisition to the Defense Personnel Support Center, Philadelphia (S9M) or by passing the requisition data by telephone to Customer Service, Directorate of Medical Material, Defense Personnel Support Center, at Commercial (215) 952-2111/2/3/4/5 or AUTOVON 444 + extension (service available 24 hours a day, 7 days a week).

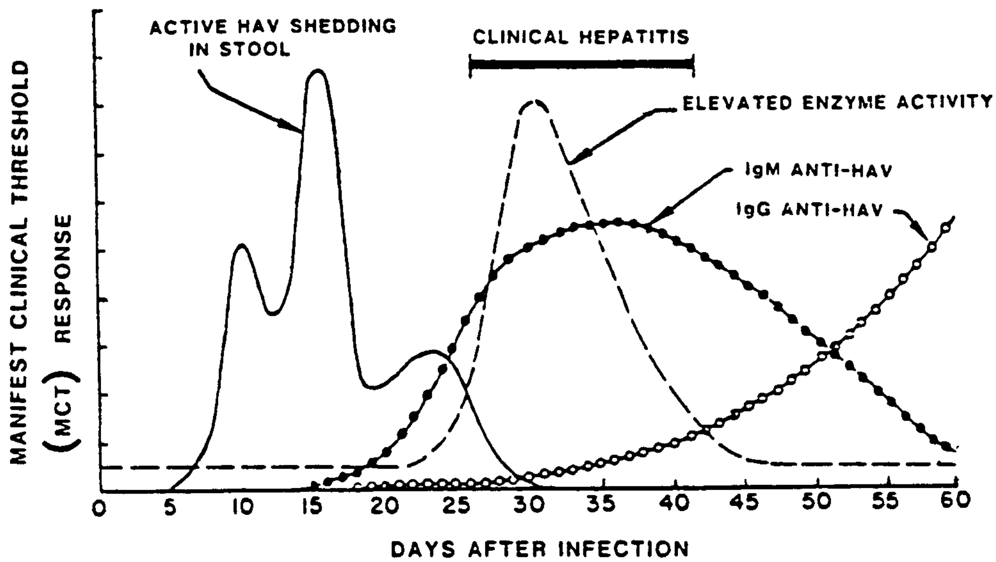
ALGORITHM FOR PROPHYLAXIS INVOLVING HEPATITIS IN FOOD HANDLERS



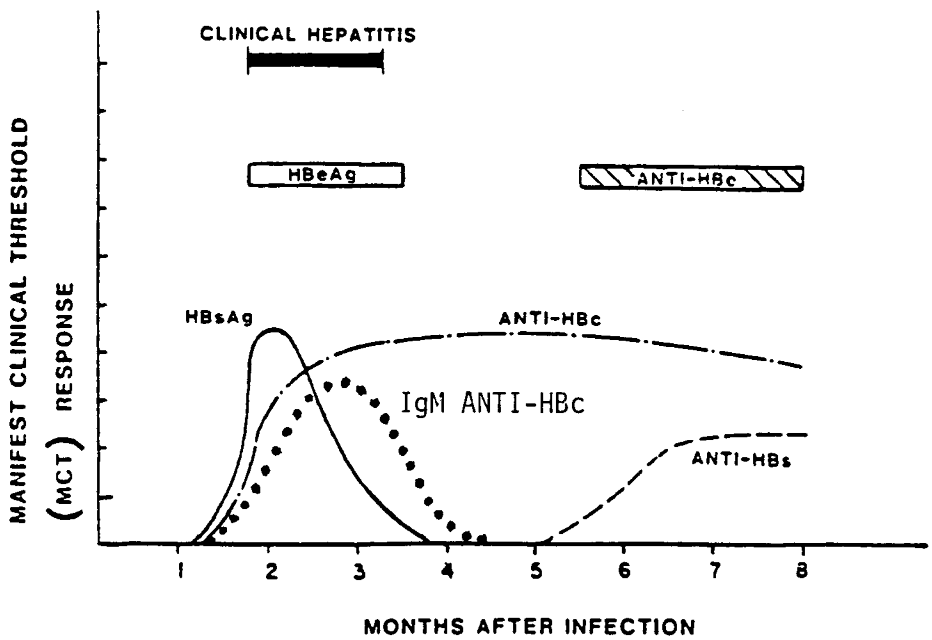

†If food handler is HBsAg-positive and IgM-anti-HAV-positive, this indicates a case of hepatitis A in a hepatitis B carrier.

*Adapted from Hepatitis Surveillance. Center for Disease Control, U.S. Department of Health and Human Services, Public Health Services: Report Number 45, May 1980.*

GRAPHIC PRESENTATION OF SEROLOGICAL MARKERS, CLINICAL SYMPTOMS, AND TRANSMISSION OF VIRAL HEPATITIS




Response to infection by hepatitis A virus in clinical cases.




Serologic responses of an individual with acute clinical HBV.

Adapted from : Maynard J.E., Hepatitis. In: Last JM (ed). Maxey-Rosenau Public Health and Preventive Medicine, 11th Ed. Appleton-Century-Crofts, New York 1980, 152-165